New Sources of Chemical Diversity Inspired by Biosynthesis: Rational Design of a Potent Epothilone Analogue

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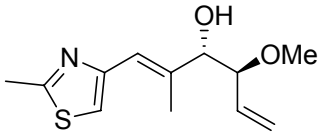
General Information:

Unless otherwise noted, all materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame dried glassware under nitrogen or argon. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and toluene were filtered through activated alumina under nitrogen. Pentane and triethylamine (NEt_3) were dried over $LiAlH_4$ and CaH_2, respectively, and distilled prior to use. 4 Å molecular sieves were oven-dried overnight and cooled under high vacuum prior to use. Dimethylformamide (DMF) was purchased from Sigma Aldrich. Thionyl chloride ($SOCl_2$) was distilled prior to use. All reactions were monitored by either E. Merck analytical thin layer chromatography (TLC) plates (silica gel 60 GF, glass back) or Whatman UV active aluminum backed TLC plates (silica gel 250 μm) and analyzed with 254 nm UV light and/or *p*-anisaldehyde/sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from E. Merck (Silica Gel 60, 230-400 mesh). Biotage chromatography was performed using Flash 40+M, 25+M, 25+S, or 12+M KP-Sil™ Silica Cartridges (32-63 μm, 60 Å, nominally 500 m^2/g silica). All ^{1}H and ^{13}C NMR spectra were obtained either on a Varian Unity Plus 300 spectrometer (operating at 299.701 MHz for ^{1}H and 75.367 MHz for ^{13}C) or on a Varian INOVA 500 spectrometer (operating at 499.864 MHz for ^{1}H and 125.690 MHz for ^{13}C) or on a Varian INOVA 600 spectrometer (operating at 599.879 MHz for ^{1}H and 150.839 MHz for ^{13}C). Chemical shifts were reported as δ-values in parts per million (ppm) relative to residual $CHCl_3$ as internal reference (^{1}H: δ7.27, ^{13}C: δ77.23) and coupling constants (*J*) were reported in Hertz (Hz). Peak multiplicities are indicated as follows: s (singlet), d (doublet), t

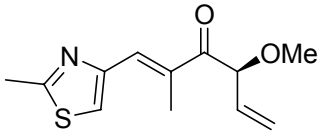
(triplet), q (quartet), and b (broad). FTIR spectra were obtained on Perkin-Elmer Paragon 1000 spectrometer and absorption frequencies were reported in reciprocal centimenters (cm^{-1}). Mass spectra (CI/EI/FAB) were obtained at the Department of Chemistry and Biochemistry, University of Notre Dame using either JEOL AX505HA or JEOL JMS-GCmate mass spectrometer.



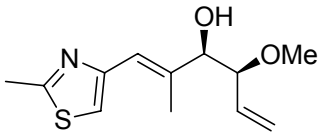
(**4**): To a stirred solution of allyl methyl ether (2.8 mL, 29.9 mmol) in 100 mL of THF at -78 ˚C was added dropwise *s*-BuLi (1.0M in cyclohexane, 24 mL, 23.9 mmol). The solution was stirred at the same temperature for 0.5 h then a 1M solution of (+)-$Ipc_2B(OMe)$ (7.6 g, 23.9 mmol) in THF was added dropwise. The reaction was left to stir at this temperature for 1 h After 1 h, BF_3•OEt_2 was added dropwise, followed by a solution the of **3**[1] (4.0 g, 23.9 mmol) in 20 mL of THF and the reaction was left to stir at -78 ˚C for 12 h. The reaction was quenched by the addition of 3.0 M NaOH (10.4 mL) and H_2O_2 (30 % in H_2O, 4.5 mL, 31.1 mmol). The reaction was warmed to ambient temperature and stirred for 4 h. The solution was diluted with Et_2O and slowly added to a solution of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was further extracted with Et_2O (3x). The organic layers were combined and washed with sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude residue was purified with column chromatography using 1:1 EtOAc:Hexanes as eluent to afford 5.0 g (88%, Mosher's ester analysis revealed >99% *ee*) of **4**, as a yellow oil. R_f = 0.24 (1:1 EtOAc:Hexanes); $[\alpha]^{20}_D$ +15.8 (*c* = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.95

[1] Nicolaou, K. C., Ninkovic, S., Sarabia, F., Vourloumis, D., He, Y., Vallberg, H., Finlay, M. R. V., Yang, Z.; *J. Am. Chem. Soc.* **1997**, *119*, 7974-7991.

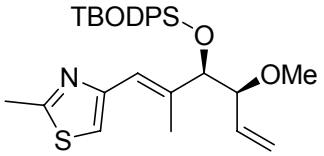
(1H, s), 6.54 (1H, s), 5.62 (1H, ddd, J = 7.8, 11.0, 16.6), 5.26 (1H, d, J = 16.6), 5.24 (1H, d, J = 10.8), 4.03 (1H, d, J = 7.8), 3.60 (1H, t, J = 7.8), 3.35 (3H, s), 3.05 (1H, bs), 2.70 (3H, s), 2.03 (3H, d, J = 1.4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 152.9, 137.6, 134.5, 122.6, 120.0, 116.2, 85.4, 80.5, 56.9, 19.5, 14.9; IR (NaCl, neat) 3430, 2980, 2927, 2824, 1645, 1506 cm^{-1}; HRMS (FAB+) Calcd for $C_{12}H_{18}NO_2S$, 240.1058. Found 240.1062.



(**E-1**): To a solution of **4** (4.7 g, 19.5 mmol), $NaHCO_3$ (1.0 g), and 350 mL of CH_2Cl_2 at 0 ˚C was added portionwise Dess-Martin periodinane (12.5 g, 29.5 mmol) over 30 min. The reaction was stirred at 0 ˚C for 6 h and then quenched by the slow addition a 1:1 solution of sat. aq. $NaHCO_3/Na_2S_2O_3$. The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2x). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude residue was purified on column chromatography using 1:3 EtOAc:Hexanes as eluent to afford 4.4 g (95%) of **E-1**, as a yellow oil. R_f = 0.44 (1:1 EtOAc:Hexanes); $[\alpha]^{20}_D$ -2.9 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (1H, s), 7.37 (1H, s), 5.93 (1H, ddd, J = 6.2, 10.6, 17.1), 5.47 (1H, d, J = 17.3), 5.35 (1H, d, J = 10.4), 4.87 (1H, d, J = 6.6), 3.40 (3H, s), 2.76 (3H, s), 2.26 (3H,s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 165.8, 151.9, 135.5, 134.1, 132.8, 122.4, 119.7, 85.3, 57.3, 19.6, 14.1; IR (NaCl, neat) 3097, 2985, 2928, 2824, 1732, 1671, 1445, 1201, 1134 cm^{-1}; HRMS (FAB+) Calcd for $C_{12}H_{16}NO_2S$, 238.0902. Found 238.0895.

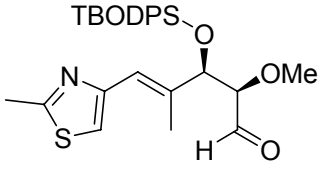


(**5**): To a solution of **E-1** (4.0 g, 16.9 mmol) in 300 mL of MeOH at -15 ˚C was added $CeCl_3$•$7H_2O$ (9.42 g, 25.3 mmol). The reaction was stirred at this temperature for 15 min., then $NaBH_4$ (0.7 g, 18.5 mmol) was added in small portions. The reaction was maintained at this temperature until complete (~6 h), then quenched with H_2O and allowed to reach ambient temperature. The layers were separated and the aqueous layer was further extracted with Et_2O (3x). The organic layers were combined and dried over $MgSO_4$. The organic layer was filtered and concentrated under vacuum. The residue was purified on column chromatography using 1:1 EtOAc:Hexanes as eluent to afford 3.9 g (96%, *dr*: 93:7, *ee*: 95%, Mosher's ester analysis) of **5**, as a yellow oil. R_f = 0.28 (1:1 EtOAc:Hexanes); $[\alpha]^{20}_D$ +10.1 (*c* = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (1H, s), 6.58 (1H, s), 5.77 (1H, ddd, *J* = 7.8, 10.6, 18.2), 5.34 (1H, d, *J* = 10.8), 5.31 (1H, d, *J* = 17.9), 4.30 (1H, d, *J* = 4.6), 3.76 (1H, dd, *J* = 4.8, 7.8), 3.34 (3H, s), 2.71 (3H, s), 2.50 (1H, bs), 2.07 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 153.2, 138.1, 134.1, 120.5, 120.2, 116.0, 84.6, 78.0, 56.9, 19.5, 15.7; IR (NaCl, neat) 3400, 2982, 2927, 2823, 1644, 1506, 1188 cm^{-1}; HRMS (FAB+) Calcd for $C_{12}H_{18}NO_2S$, 240.1071. Found 240.1058.



(**E-2**): To a solution of **5** (3.9 g, 16.2 mmol) in 100 mL of DMF at 0 ˚C was added imidazole (5.5 g, 81.0 mmol) and the reaction was stirred until homogenous. To the reaction was added a solution of TBODPSCl (14.1 g, 48.6 mmol) in 20 mL of DMF dropwise over 30 minutes. The reaction was allowed to reach room temperature while stirring overnight.

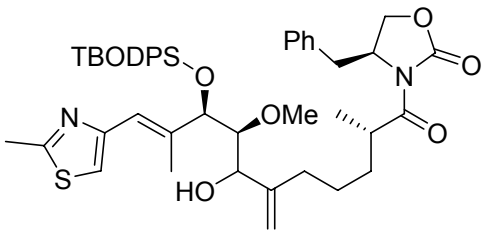
The reaction was quenched by the slow addition of sat. aq. NH_4Cl and was further diluted with Et_2O. The layers were separated and the aqueous layer was further extracted with Et_2O (4x). The organic layers were combined and washed successively with sat. aq. NH_4Cl (2x) and H_2O (2x). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude oil was purified on column chromatography using 1:9 EtOAc:Hexanes to afford 7.9 g (98%) of **E-2**, as a clear oil. R_f = 0.20 (1:9 EtOAc:Hexanes); $[\alpha]^{20}_D$ -22.3 (*c* = 3.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.66 (m, 4H), 7.25-7.41 (m, 6H), 6.76 (1H, s), 6.40 (1H, s), 5.74 (1H, ddd, *J* = 7.8, 10.6, 17.3), 5.26 (1H, d, *J* = 11.0), 5.23 (1H, d, *J* = 17.7), 4.34 (1H, d, *J* = 5.8), 3.65 (1H, dd, *J* = 6.0, 7.8), 3.21 (3H, s), 2.70 (3H, s), 1.95 (3H, d, *J* = 1.2), 1.25 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 153.3, 139.2, 136.3, 135.6, 135.6, 135.5, 135.5, 130.0, 129.8, 127.6, 127.5, 122.2, 119.3, 115.7, 85.5, 80.8, 74.1, 56.9, 32.1, 19.5, 15.3; IR (NaCl, neat) 3070, 3050, 2978, 2927, 2820, 1430, 1365, 1184, 1114, 1088, 1058 cm^{-1}; HRMS (FAB+) Calcd for $C_{28}H_{36}O_3NSSi$, 494.2185. Found 494.2158.

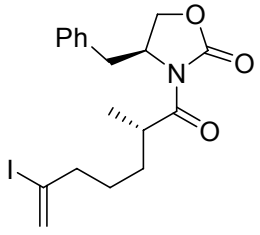


(**6**): To a solution of **E-2** (8.0 g, 16.2 mmol) in 160 mL of *t*-BuOH, 160 mL of THF, and 27 mL of H_2O at 0 ˚C was added NMO (3.8 g, 32.4 mmol). The reaction was stirred until a homogenous solution was achieved then OsO_4 (0.01 g, 0.4 mmol) was added and the reaction was allowed to reach ambient temperature while stirring overnight. The reaction was saturated with solid $Na_2S_2O_3$ and stirred for an additional 4 h. The reaction was diluted with EtOAc and brine and further extracted with EtOAc (3x). The organic layers

were combined and dried over $MgSO_4$. The slurry was filtered and the filtrate was concentrated under vacuum to yield the crude diol.

The crude diol was diluted with 320 mL of CH_2Cl_2 and cooled to 0 ˚C. To the chilled solution was added 3.0 g of $NaHCO_3$ (35.4 mmol) followed by portionwise addition of 7.9 g of $Pb(OAc)_4$ (17.7 mmol). The reaction was stirred at 0 ˚C for 1 h, then filtered through a glass frit funnel. The filtrate was diluted with sat. aq. $NaHCO_3$ and the layers were separated. The aqueous layer was further extracted with Et_2O (3x). The organic layers were combined, dried over $MgSO_4$, and filtered. The filtrate was concentrated under vacuum and the residue was purified on column chromatography using 1:3 EtOAc:Hexanes as eluent to afford 5.6 g (70%) of **6**, as a clear oil. $R_f = 0.51$ (1:1 EtOAc:Hexanes); $[\alpha]^{20}_D$ -30.1 (c = 9.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (1H, d, J = 3.0), 7.61 (4H, m), 7.26-7.42 (6H, m), 6.77 (1H, s), 6.45 (1H, s), 4.61 (1H, d, J = 6.0), 3.68 (1H, ddd, J = 2.8, 6.0), 3.34 (3H, s), 2.70 (3H, s), 1.97 (3H, s), 1.24 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 152.8, 137.1, 135.5, 135.4, 134.6, 134.6, 130.3, 130.2, 127.9, 127.7, 122.8, 116.6, 87.4, 78.2, 74.5, 58.9, 32.1, 19.5, 15.1; IR (NaCl, neat) 2975, 2929, 2829, 1736, 1430, 1184, 1115, 1058 cm^{-1}; HRMS (FAB+) Calcd for $C_{27}H_{34}O_4NSSi$, 496.1978. Found 496.1979.



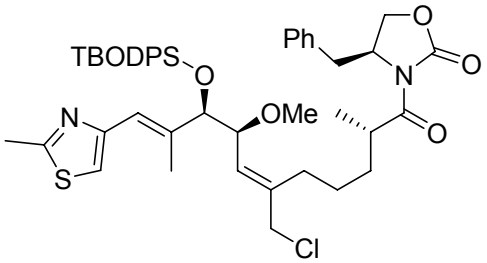


(Ref. 2)

(**E-3**): Under an inert atmosphere, 1.4 g of $CrCl_2$ (11.3 mmol) loaded with 1 mol% $NiCl_2$ was added to a flask. To this flask was added via cannula 20 mL of dry DMF:THF (3:1)

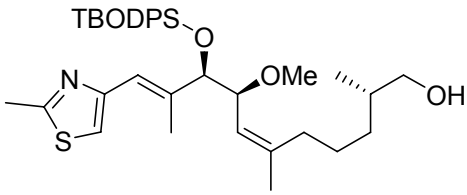
solution. The reaction was cooled to 0 ˚C and a solution containing 1.1 g of **6** (2.3 mmol) and 1.9 g of **7**[2] (4.5 mmol) in 10 mL of dry DMF:THF (3:1) was added dropwise via cannula. After addition, the reaction was allowed to reach ambient temperature and continued to stir for additional 6 h. The reaction was diluted with Et_2O and sat. aq. NH_4Cl. The layers were separated and the aqueous layer was further extracted with Et_2O (3x). The organic layers were combined and dried over $MgSO_4$. The slurry was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified on column chromatography using 1:3 EtOAc:Hexanes as eluent to afford 1.4 g (78%, 3:1 dr) of **E-3**, as a clear semi-solid. R_f = 0.56 (1:1 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, characteristic peaks for mixture of diastereomers) δ 7.61-7.68 (m), 7.20-7.42 (m), 6.77 (s), 6.72 (s), 6.45 (s), 5.13 (s), 5.06 (s), 4.92 (s), 4.89 (s), 4.65 (m), 4.58 (d, *J* = 5.0), 4.48 (d, *J* = 6.5), 4.30 (d, *J* = 4.0), 4.12-4.21 (m), 4.02 (d, *J* = 8.0), 3.72 (m), 3.35 (s), 3.32 (s), 3.22-3.34 (m), 2.78 (m), 2.69 (s), 1.90-2.21 (m), 2.0 (s), 1.91 (s), 1.75-1.81 (m), 1.36-1.50 (m), 1.24 (s), 1.23 (s), 1.22 (d, *J* = 7.0) ; ^{13}C NMR (125 MHz, $CDCl_3$, characteristic peaks for mixture of diastereomers) δ 177.2, 177.1, 164.0, 153.1, 152.9, 149.5, 148.9, 138.9, 138.6, 135.4, 135.3, 135.2, 134.8, 134.7, 134.6, 134.5, 130.1, 130.0, 130.0, 129.8, 129.5, 128.9, 127.7, 127.6, 127.5, 127.4, 127.3, 122.6, 122.2, 115.6, 115.6, 111.8, 110.8, 85.4, 83.7, 80.4, 77.8, 75.4, 74.2, 74.1, 72.0, 66.0, 60.7, 60.2, 55.4, 37.9, 37.7, 37.6, 33.1, 32.5, 32.2, 31.8, 31.8, 25.4, 25.3, 19.2, 17.5, 17.4, 15.6; IR (NaCl, neat) 3513, 2975, 2930, 1781, 1698, 1388, 1122, 1056 cm^{-1}; HRMS (FAB+) Calcd for $C_{45}H_{57}O_7N_2SSi$, 796.3578. Found 796.3582.

[2] Taylor, R. E., Chen, Y. *Org. Lett.* **2001**, *3*, 2221.

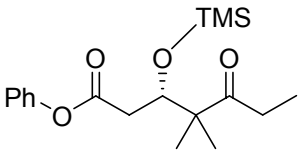


(**8**): To a solution of 1.1 g of **E-3** (1.4 mmol) in 100 mL of Et_2O:pentane (1:3) at -78 ˚C was added over 1 minute via cannula a precooled (-78 ˚C) solution of 0.55 mL of freshly distilled $SOCl_2$ (7.0 mmol) in 40 mL Et_2O:pentane (1:3). The reaction was maintained at the same temperature for 2h then slowly warmed to room temperature over 5h. The reaction was recooled to -78 ˚C and 3.9 mL of NEt_3 (28.0 mmol) was added. The solution was diluted with sat. aq. NH_4Cl and Et_2O, warmed to room temperature and stirred for 1h. The layers were separated and the aqueous layer was further extracted with Et_2O (3x). The organic layers were combined and dried over $MgSO_4$. The slurry was filtered and the filtrate was concentrated under vacuum. The residue was purified on column chromatography using 1:3 EtOAc:Hexanes as eluent to afford 0.9 g (80%) of **8**, as a thick oil. R_f = 0.59 (1:1 EtOAc:Hexanes); $[\alpha]^{20}_D$ +22.2 (*c* = 0.67, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (4H, d, *J* = 6.5), 7.23-7.41 (10H, m), 7.20 (1H, d, *J* = 6.5), 6.80 (1H, s), 6.43 (1H, s), 5.40 (1H, d, *J* = 9.5), 4.61 (1H, dddd, *J* = 3.0, 3.0, 6.0, 10.5), 4.36 (1H, d, *J* = 6.0), 4.12 (2H, m), 3.99 (2H, m), 3.67 (1H, m), 3.24 (1H, dd, *J* = 3.0, 13.0), 3.16 (3H, s), 2.75 (1H, dd, *J* = 10.0, 13.5), 2.70 (3H, s), 2.17 (2H, m), 1.98 (3H, s), 1.72 (1H, m), 1.34-1.44 (4H, m), 1.22 (9H, s), 1.17 (3H, d, *J* = 3.9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 164.0, 153.0, 152.9, 140.4, 138.8, 135.4, 135.3, 135.2, 135.2, 129.8, 129.6, 129.5, 129.4, 128.9, 127.4, 127.3, 127.3, 122.2, 115.6, 80.0, 78.9, 77.2, 73.9, 66.0, 56.4, 55.3, 49.3, 37.9, 37.5, 33.2, 31.9, 28.3, 25.6, 19.2, 17.5, 15.3; IR (NaCl, neat) 3069, 2972, 2927, 1780, 1698, 1386,

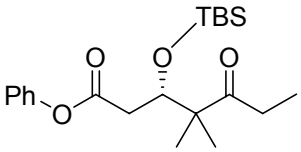
1114, 1056 cm^{-1}; HRMS (FAB+) Calcd for $C_{45}H_{56}ClO_6N_2SSi$, 815.3317. Found 815.3341.



(**E-4**): To a solution of 560 mg of **8** (0.68 mmol) in 40 mL of THF at -78 ˚C was added over 40 minutes via a syringe pump 6.8 mL of $LiHBEt_3$ (1.0 M in THF, 3.4 mmol). After addition was complete, the reaction was maintained at this temperature for 2h then warmed slowly to room temperature over 4h. The solution was diluted with Et_2O, followed by the slow addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined and washed with sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified on column chromatography using 1:3 EtOAc:Hexanes as eluent to afford 355 mg (81%) of **E-4**, as a thick oil. R_f = 0.50 (1:1 EtOAc:Hexanes); $[\alpha]^{20}_D$ -12.1 (*c* = 1.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (4H, m), 7.25-7.42 (6H, m), 6.79 (1H, s), 6.43 (1H, s), 5.10 (1H, d, *J* = 9.5), 4.36 (1H, d, *J* = 5.2), 3.99 (1H, dd, *J* = 5.3, 9.5), 3.42 (2H, dddd, *J* = 6.0, 6.0, 16.5, 16.5), 3.19 (3H, s), 2.72 (3H, s), 2.02 (2H, m), 1.98 (3H, s), 1.74 (3H, s), 1.28-1.58 (4H, m), 1.26 (9H, s), 1.03-1.10 (2H, m), 0.90 (3H, d, *J* = 6.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 153.3, 141.6, 140.0, 135.7, 135.6, 135.6, 135.5, 129.9, 129.8, 127.6, 127.5, 124.0, 121.8, 115.4, 80.5, 79.9, 74.1, 68.3, 56.4, 36.0, 33.4, 32.9, 32.1, 25.8, 23.9, 19.4, 16.8, 15.7; IR (NaCl, neat) 3367, 3069, 2974, 2928, 1430, 1366, 1185, 1114, 1056 cm^{-1}; HRMS (FAB+) Calcd for $C_{35}H_{50}O_4NSSi$, 608.3230. Found 608.3024.



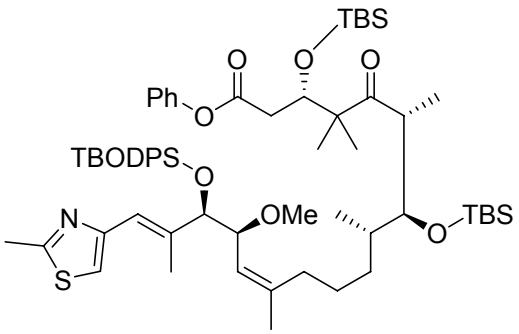
(**12**): To a solution of 3.7 g of *N*-Ts-D-Valine-H (12 mmol) in 30 mL of CH_2Cl_2 at 0 ˚C was added 12.0 mL of BH_3•THF (1.0M in THF, 12.0 mmol) dropwise over 10 minutes. The reaction mixture was stirred at 0 ˚C for 30 minutes, then warmed to room temperature and stirred for an additional 30 minutes. The solution was cooled to -78 ˚C, then 1.54 g of 2,2-dimethyl-3-oxo-pentanal[3] (12.0 mmol) in 10 mL of CH_2Cl_2 was added slowly. After stirring for 5 minutes, a solution of 2.08 g of trimethyl-(1-phenoxy-vinyloxy)-silane[4] (10.0 mmol) in 10 mL of CH_2Cl_2 was added dropwise over 10 minutes. The reaction was stirred at -78 ˚C for 2h and then quenched with sat. aq. $NaHCO_3$. The reaction was warmed to room temperature and stirred for an additional 30 minutes. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined and dried over $MgSO_4$. The slurry was filtered, concentrated and purified on column chromatography using 1:2 Et_2O:Hexanes as eluent to afford 2.3 g (69%) of **12**, as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.10 (5H, m), 4.53 (1H, dd, *J* = 3.0, 8.1), 2.74-2.52 (4H, m), 1.21 (3H, s), 1.18 (3H, s), 1.04 (3H, t, *J* = 7.2), 0.15 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.6, 170.8, 150.8, 129.6, 126.0, 121.7, 74.3, 52.3, 39.3, 32.4, 21.5, 20.8, 7.9, 0.6.



(**13**): To a solution of 0.34 g of **12** (1.0 mmol) in 10 mL of CH_2Cl_2/THF (1:1) was added 0.4 mL of CF_3COOH and 0.04 mL of H_2O. The reaction was stirred at room temperature for 2h,

[3] Inukai, T., Yoshizawa, R. *J. Org. Chem.* **1967**, *32*, 404-407.
[4] Bieniek, A., Epsztajn, J., Kulikiewicz, K. K.; *Syn. Commun.* **2003**, *33*, 667-677.

then all the volatiles were removed completely under reduced pressure. The crude product was dissolved in 5 mL of CH_2Cl_2 and then 0.23 mL of 2,6-lutidine (2.0 mmol) followed by 0.42 mL of TBSOTf (1.2 mmol) were added dropwise. The reaction was stirred at room temperature for 1h, then the solvent was removed under reduced pressure and the residue was purified on column chromatography using 1:2 Et_2O:Hexanes as eluent to afford 0.34 g (91%) of **13**, as a colorless oil. R_f = 0.37 (1:10 EtOAc:Hexanes); $[\alpha]^{20}_D$ -18.9 (*c* = 2.0, THF); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 7.5), 7.23 (1H, m), 7.09 (2H, d, *J* = 7.5), 4.58 (1H, dd, *J* = 3.6, 6.6), 2.74 (1H, dd, *J* = 4.2, 16.8), 2.50-2.60 (2H, m), 1.22 (3H, s), 1.18 (3H, s), 1.05 (3H, t, *J* = 7.2), 0.91 (9H, s), 0.12 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 170.8, 150.8, 129.6, 126.0, 121.7, 73.7, 52.8, 39.8, 32.0, 26.1, 21.4, 20.7, 18.3, 7.9, -4.1, -4.8; IR (NaCl, neat) 2932, 2857, 1759, 1702, 1593, 1493, 1472, 1089, 836, 777 cm^{-1}.



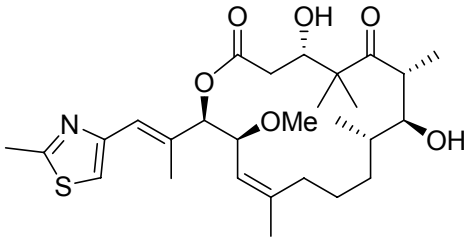
(**E-5**): To a solution of 310 mg of **E-4** (0.51 mmol) and 210 mg of $NaHCO_3$ (2.6 mmol) in 20 mL of CH_2Cl_2 at 0 ˚C was added portionwise 300 mg of Dess-Martin periodinane (0.71 mmol). The reaction was stirred at 0 ˚C for 3h then quenched with sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3x). The organic layers were combined and dried over $MgSO_4$. The slurry was filtered and the filtrate was concentrated under vacuum. The crude residue was diluted with hexanes and filtered

through a plug of Celite, using hexanes as eluent. The hexanes was then removed under vacuum to afford the relatively pure **9**, which was used without further purification.

To a solution of 260 mg of **13** (0.7 mmol) in 15 mL of CH_2Cl_2 at -78 ˚C was added dropwise a 1M solution of $TiCl_4$ (0.74 mL, 0.74 mmol) in CH_2Cl_2. The bright yellow-orange solution was stirred for 2 minutes, then 0.13 mL of EtN*i*Pr_2 (0.74 mmol) was added and the dark red reaction was stirred at -78 ˚C for 1h. After 1h, a solution of 280 mg of **9** (0.46 mmol) in 5 mL of CH_2Cl_2 was added dropwise via cannula. The reaction was let to warm to -20 ˚C overnight (by placing the reaction in a -78 ˚C bath in a freezer at -20 ˚C and allowing to equilibrate) and was quenched with sat. aq. NH_4Cl. The layers were separated and the aqueous layer was further extracted with Et_2O (3x). The organic layers were combined and washed with sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography using 1:4 EtOAc:Hexanes as eluent to afford 360 mg (80%) of **14**, as a single diastereomer.

To a solution of 400 mg of **14** (0.41 mmol) in 15 mL of CH_2Cl_2 at 0 ˚C was added dropwise 0.3 mL of 2,6-lutidine (2.64 mmol) followed by 0.33 mL of TBSOTf (1.42 mmol). The reaction was stirred at 0 ˚C for 1h then warmed to room temperature and stirred for an additional 3h. The reaction was quenched by the addition of H_2O and extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vaccum. The crude oil was purified on column chromatography using 15% EtOAc:Hexanes to afford 430 mg (95%) of **E-5**, as a thick oil. R_f = 0.53 (1:3 EtOAc:Hexanes); $[\alpha]^{20}_D$ -17.2 (*c* = 2.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.62 (4H, m), 7.20-7.39 (9H, m), 7.10 (2H, dd, *J* = 1.0, 8.0), 6.75 (1H, s), 6.38 (1H, s), 5.00

(1H, d, J = 9.5), 4.47 (1H, dd, J = 3.5, 6.0), 4.26 (1H, d, J = 6.5), 3.96 (1H, dd, J = 6.5, 9.5), 3.80 (1H, dd, J = 1.5, 6.5), 3.16 (1H, m), 3.15 (3H, s), 2.74 (1H, dd, J = 3.5, 16.5), 2.70 (3H, s), 2.53 (1H, dd, J = 6.0, 17.0), 2.08 (1H, m), 1.96 (3H, s), 1.89 (1H, m), 1.70 (3H, s), 1.31 (3H, s), 1.22 (9H, s), 1.13 (3H, s), 1.13-1.40 (5H, m), 1.09 (3H, d, J = 7.0), 0.92 (9H, s), 0.91 (9H, s), 0.89 (3H, d, J = 8.0), 0.11 (3H, s), 0.10 (3H, s), 0.10 (3H, s), 0.07 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 222.1, 170.6, 163.9, 153.2, 150.7, 141.6, 139.4, 135.5, 135.4, 135.3, 135.3, 129.7, 129.5, 129.4, 127.3, 127.3, 125.8, 123.9, 121.9, 121.6, 121.5, 115.3, 80.6, 79.1, 77.6, 77.2, 73.8, 73.7, 56.1, 53.5, 45.3, 40.5, 38.7, 33.1, 31.8, 31.1, 26.4, 26.3, 26.1, 25.7, 23.7, 19.5, 19.2, 18.5, 18.2, 17.7, 15.5, 15.1, -3.6, -3.6, -4.2, -4.7; IR (NaCl, neat) 2955, 2930, 1762, 1692, 1472, 1365, 1253, 1195, 1113, 1058 cm^{-1}; HRMS (FAB+) Calcd for $C_{62}H_{96}O_8NSSi_3$, 1098.6165. Found 1098.6147.



(**2**): To a solution of 280 mg of **E-5** (0.26 mmol) and 2.1 g of $NaHCO_3$ (25.5 mmol) in 22 mL of THF at 0 ˚C was added dropwise 11 mL of a 30% H_2O_2 solution in H_2O. The reaction was allowed to warm to room temperature while stirring overnight. The THF was removed in *vacuo* and the aqueous layer was acidified with 2M HCl to pH = 2. The aqueous layer was extracted with EtOAc (3x). The organic layers were combined and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified on column chromatography using 1:4 Et_2O:Hexanes (with 2%

AcOH) to afford 30 mg of **E-5** and 200 mg (85%, based upon recovered **E-5**) of **E-6**, as an oil.

The 200 mg of the **E-6** (0.20 mmol) was dissolved in 5 mL of THF. The reaction was cooled to 0 ˚C and 1.2 mL of TBAF (1M in THF, 1.2 mmol) was added dropwise. The reaction was allowed to reach room temperature over 3h and stirred for an additional 4h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O (4x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude oil was purified on column chromatography using 2:1 Et_2O:Hexanes (with 4% AcOH) to afford 110 mg (75%) of **15**, as a foam.

To a solution of 70 mg of the **15** (0.091 mmol) in 20 mL of THF at 0 ˚C was added dropwise 0.15 mL of EtN*i*Pr_2 (0.82 mmol) followed 50 μL of 2,4,6-trichlorobenzoylchloride (0.27 mmol). The reaction was stirred at 0 ˚C for 1h, then diluted with 70 mL of THF. This mixture was added by syringe pump to a solution of 250 mg of DMAP (2.0 mmol) in 200 mL of toluene at 40 ˚C over 4h. After addition, the reaction was stirred at 40 ˚C for 12h, then concentrated to afford a white residue. The residue was dissolved in Et_2O and washed successively with 20% glacial AcOH, sat. aq. $NaHCO_3$, and sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified on column chromatography using 1:9 EtOAc:Hexanes as eluent to afford 55 mg (81%) of **E-7**, as a foam.

To a solution of 50 mg of **E-7** (0.067 mmol) in 2 mL of THF at 0 ˚C was added 1 mL of HF•Pyridine (65% HF in pyridine). The reaction was warmed to room temperature over 2h and stirred for an additional 12h. The reaction was carefully poured into a solution of sat. aq. $NaHCO_3$ at 0 ˚C and then diluted with EtOAc. The layers were

separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine and dried over $MgSO_4$. The slurry was filtered and the filtrate was concentrated under vacuum. The crude product was purified on column chromatography using 1:9 *i*-PrOH:Hexanes as eluent to afford 30 mg (88%) of **2**, as a white solid. R_f = 0.26 (1:1 EtOAc:Hexanes); $[\alpha]^{20}_D$ -101.8 (*c* = 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 (1H, s), 6.60 (1H, s), 5.03 (1H, d, *J* = 9.6), 5.00 (1H, d, *J* = 9.0), 4.28 (1H, d, *J* = 10.8), 4.10 (1H, dd, *J* = 9.6, 9.6), 3.79 (1H, bs), 3.69 (1H, d, *J* = 3.6), 3.19 (3H, s), 3.14 (1H, bs), 3.13 (1H, dt, *J* = 6.6, 6.6, 1.2), 2.68 (3H, s), 2.46 (1H, m), 2.41 (1H, dd, *J* = 11.4, 13.8), 2.18 (1H, dd, *J* = 3.0, 13.8), 2.11 (3H, s), 1.96 (1H, m), 1.77 (1H, m), 1.74 (3H, s), 1.71 (1H, m), 1.34 (3H, s), 1.24-1.33 (3H, m), 1.18 (3H, d, *J* = 6.6), 1.05 (3H, s), 1.01 (3H, d, *J* = 7.2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 220.9, 169.7, 165.1, 151.9, 143.3, 139.8, 124.1, 121.0, 115.9, 79.8, 77.9, 73.9, 72.1, 55.9, 53.7, 41.2, 39.7, 38.7, 32.2, 31.9, 25.3, 23.2, 22.9, 19.0, 17.4, 17.1, 15.6, 13.2; IR (NaCl, neat) 3460, 2963, 2924, 2854, 1738, 1682, 1455, 1378, 1260, 1091, 1017 cm^{-1}; HRMS (FAB+) Calcd for $C_{28}H_{44}O_6NS$, 522.2889. Found 522.29114.

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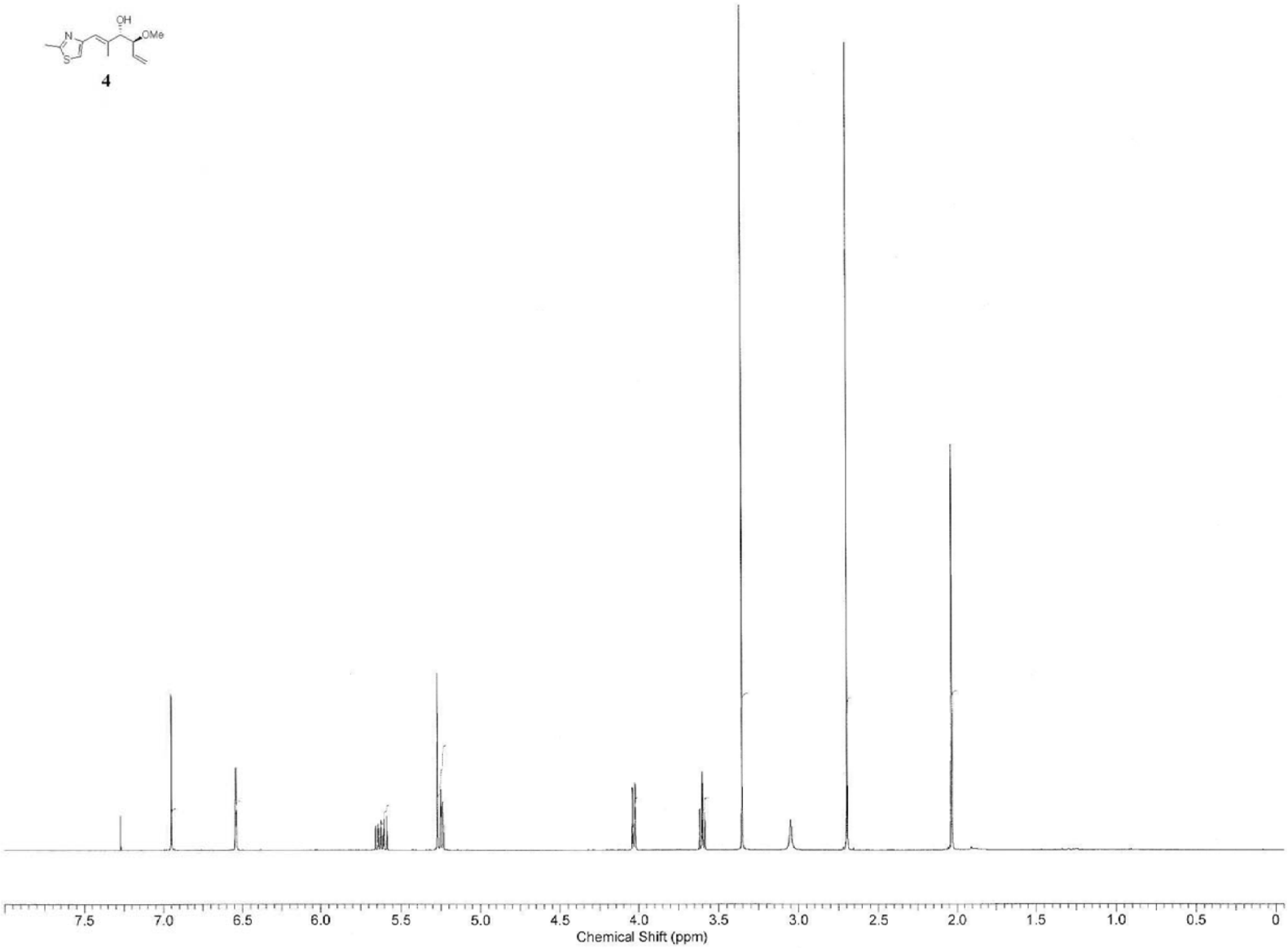
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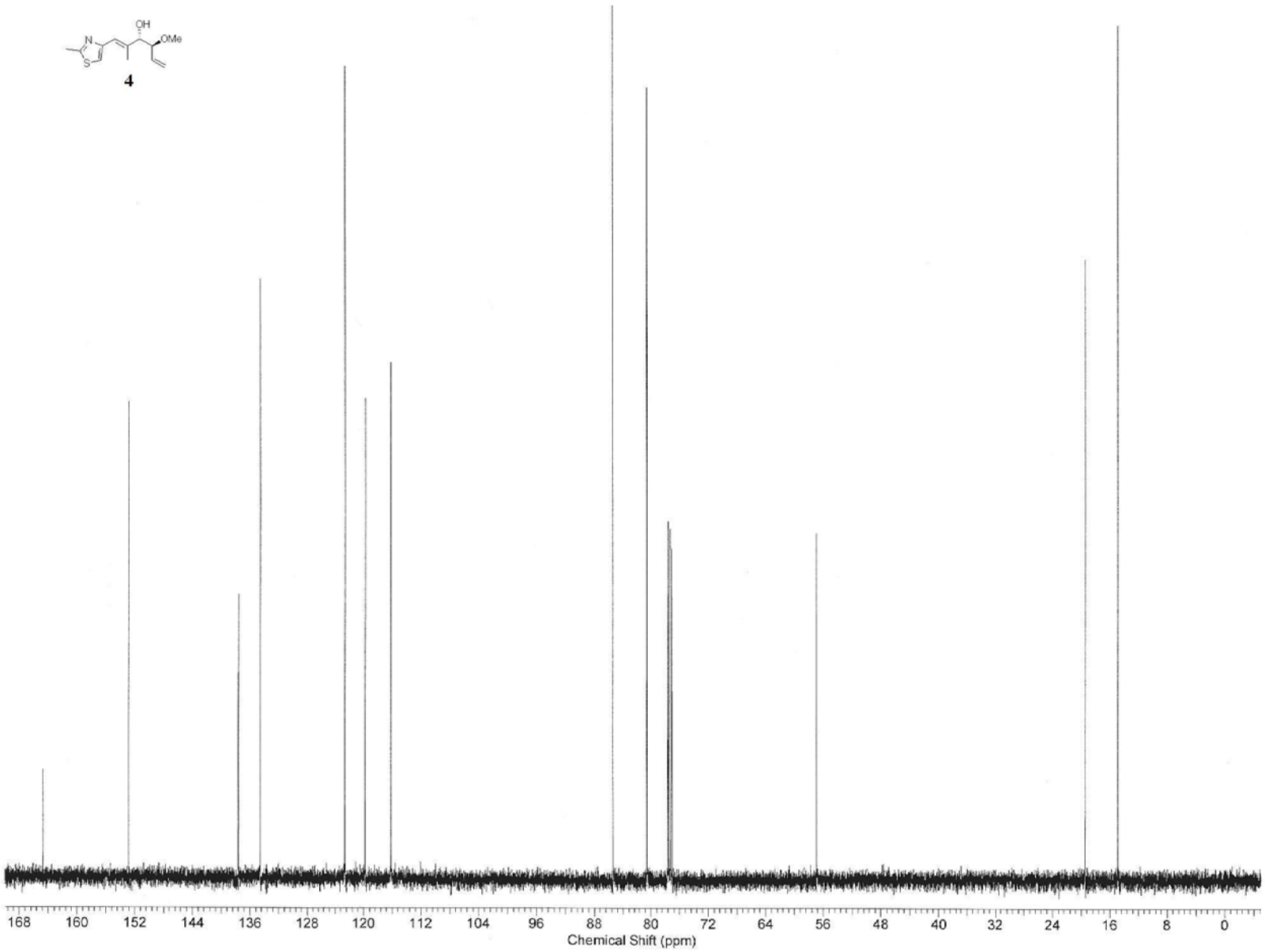
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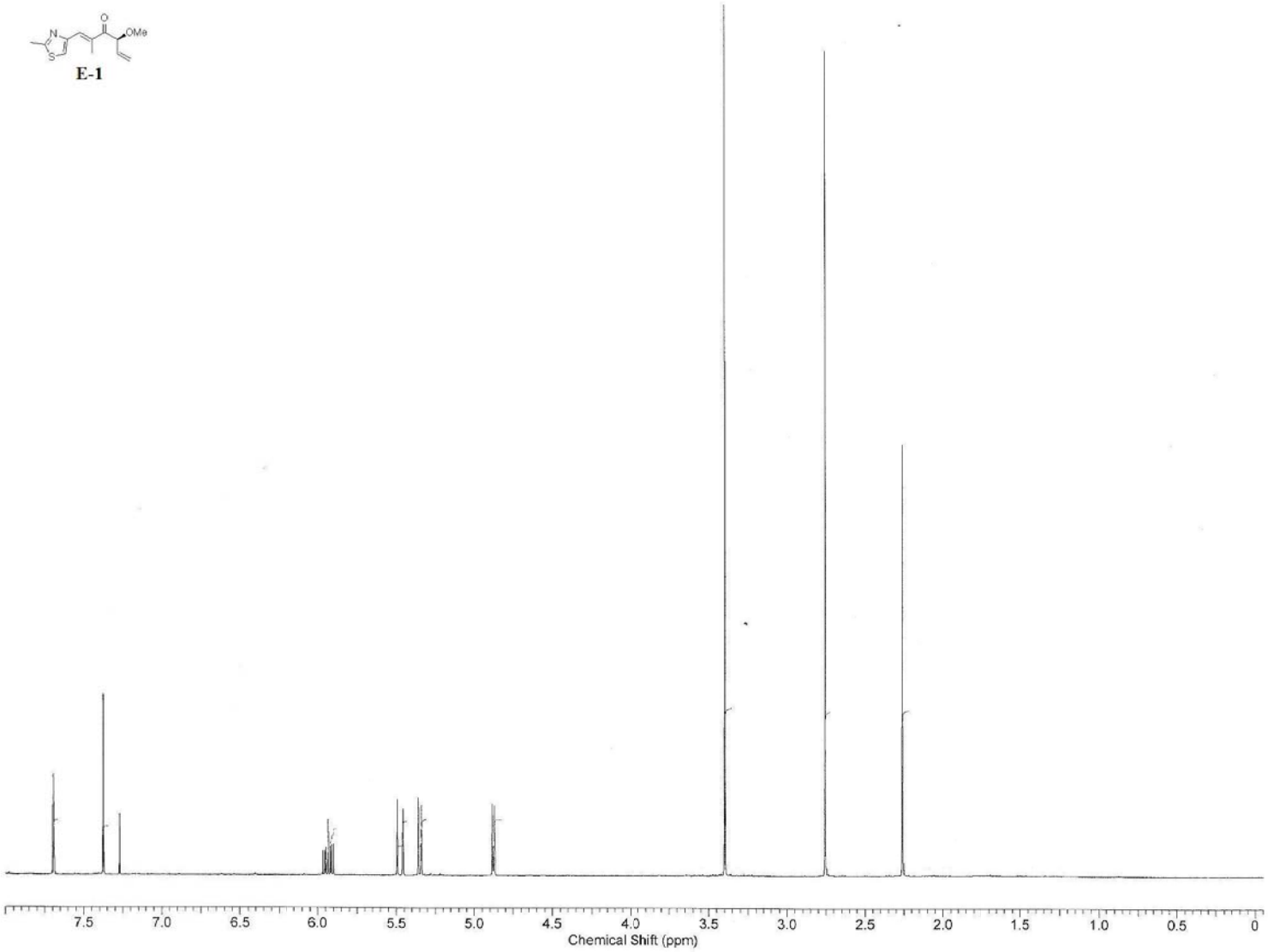
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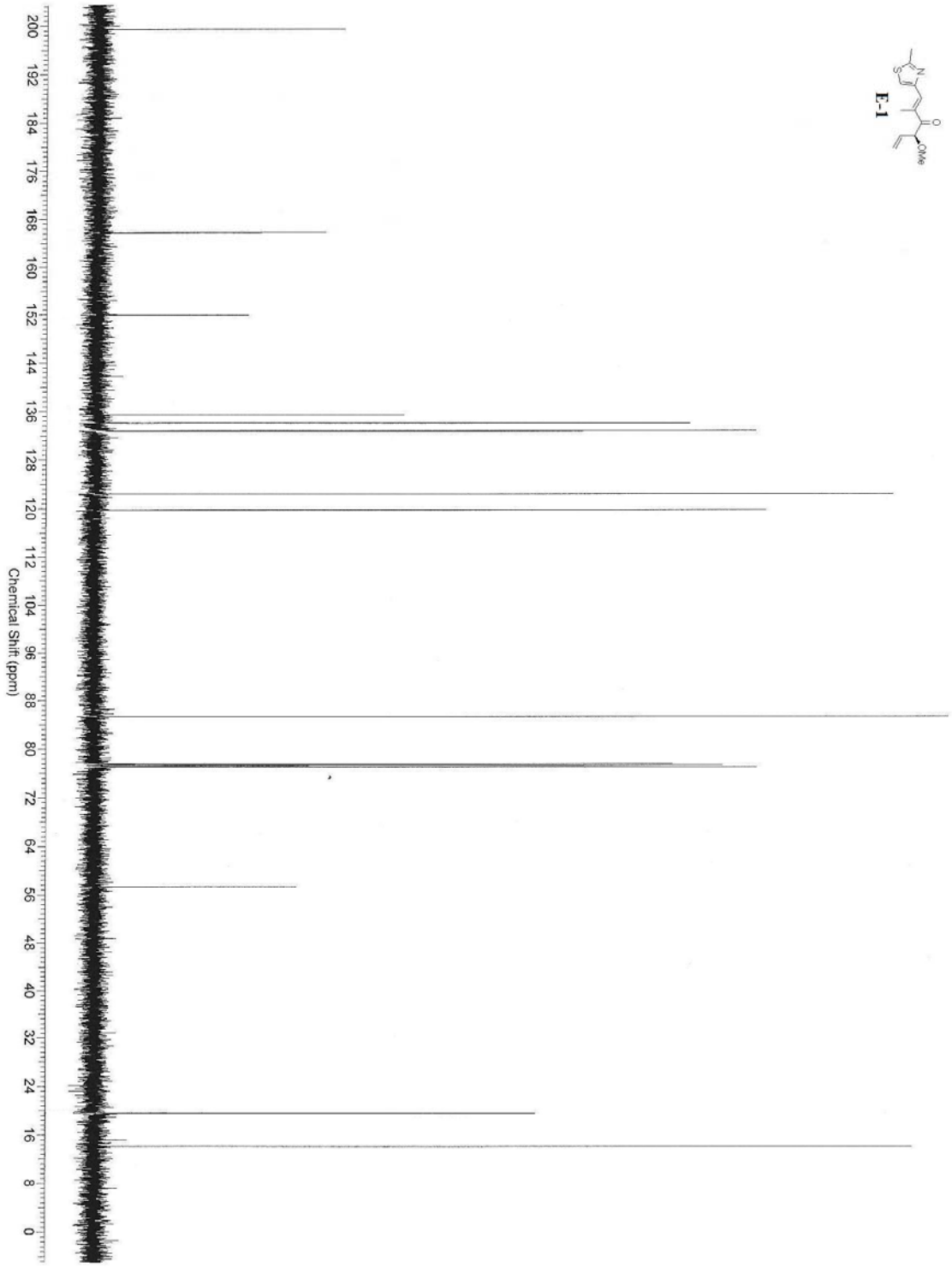
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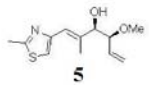
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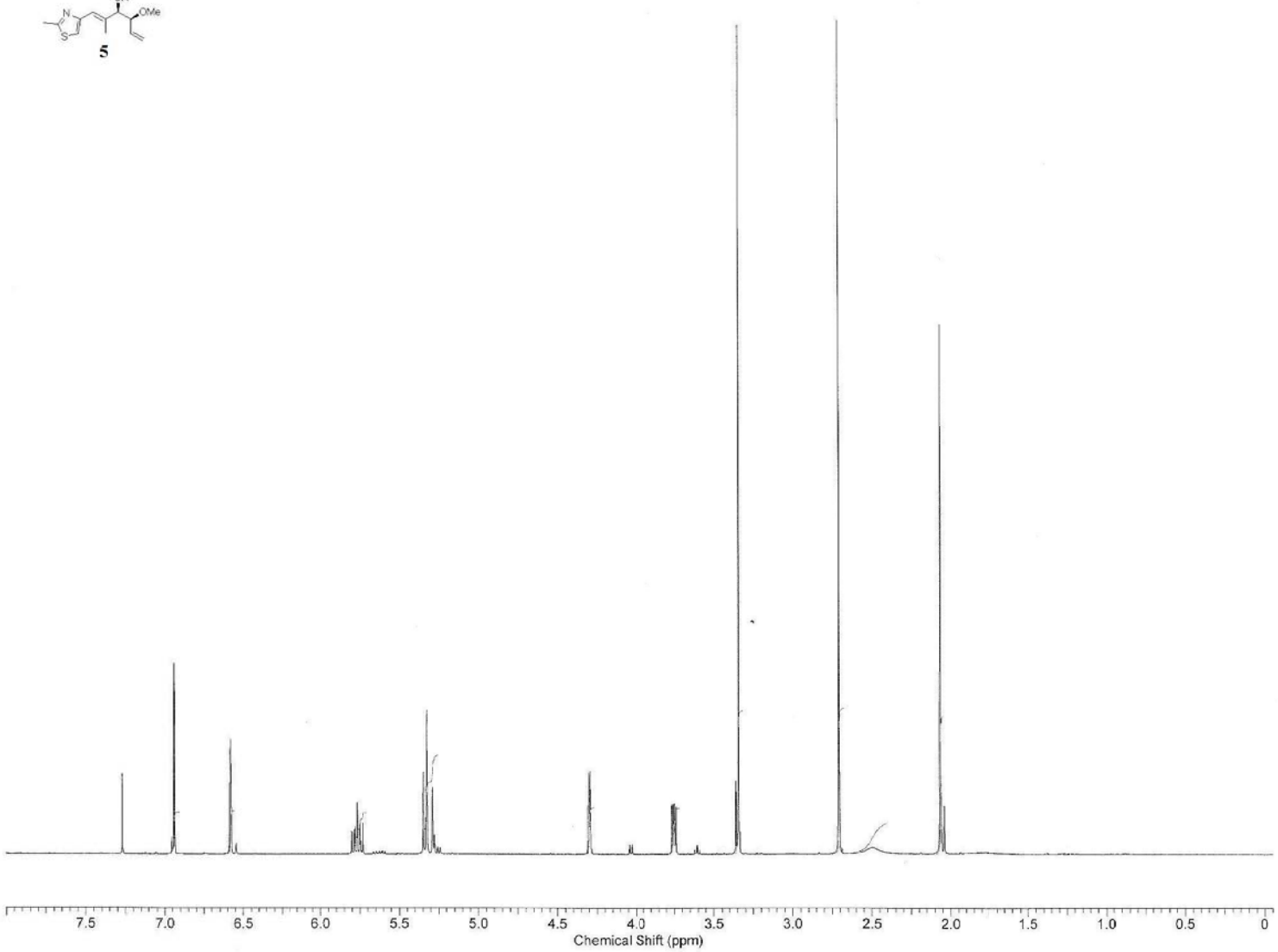
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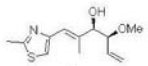
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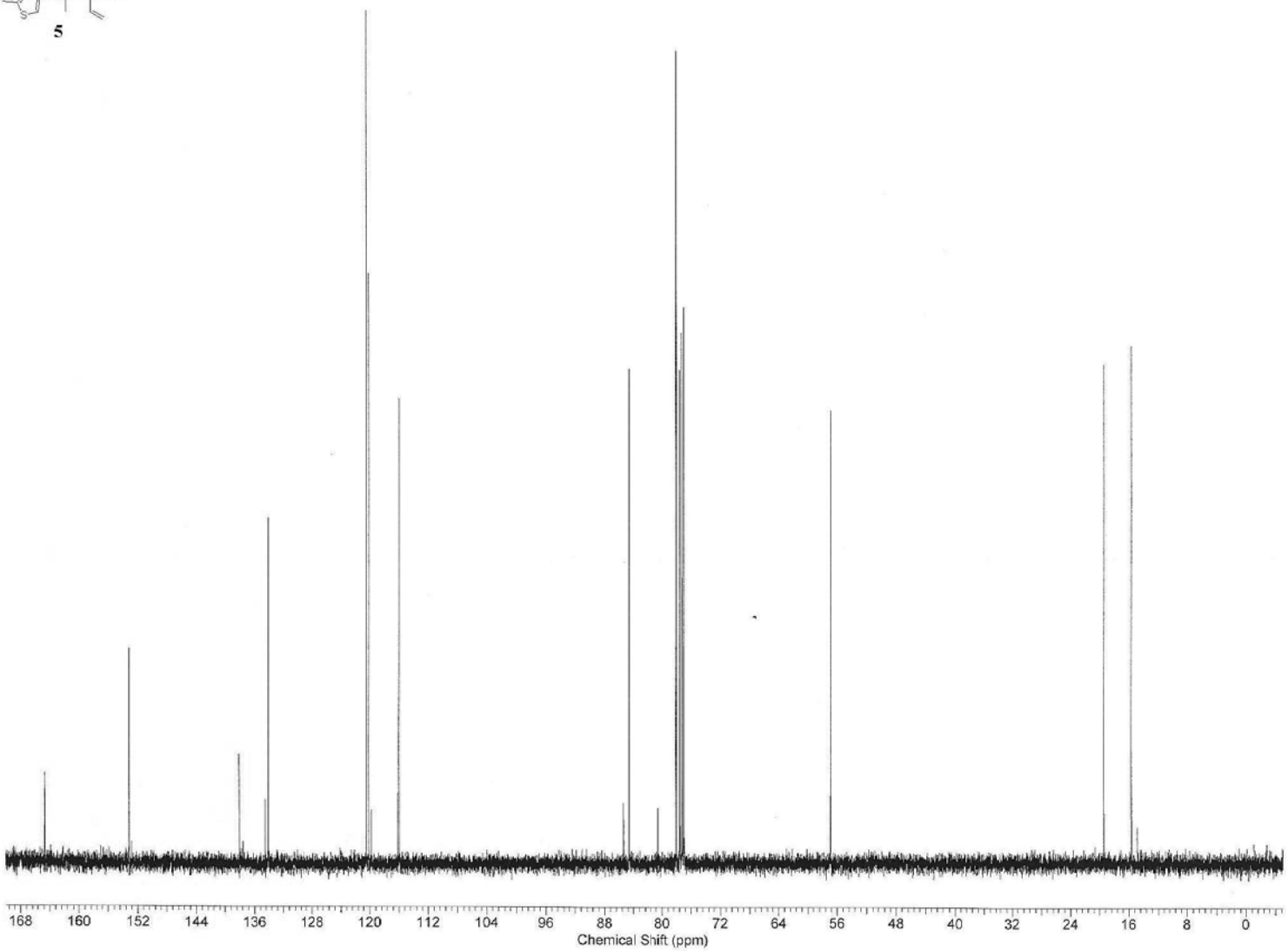
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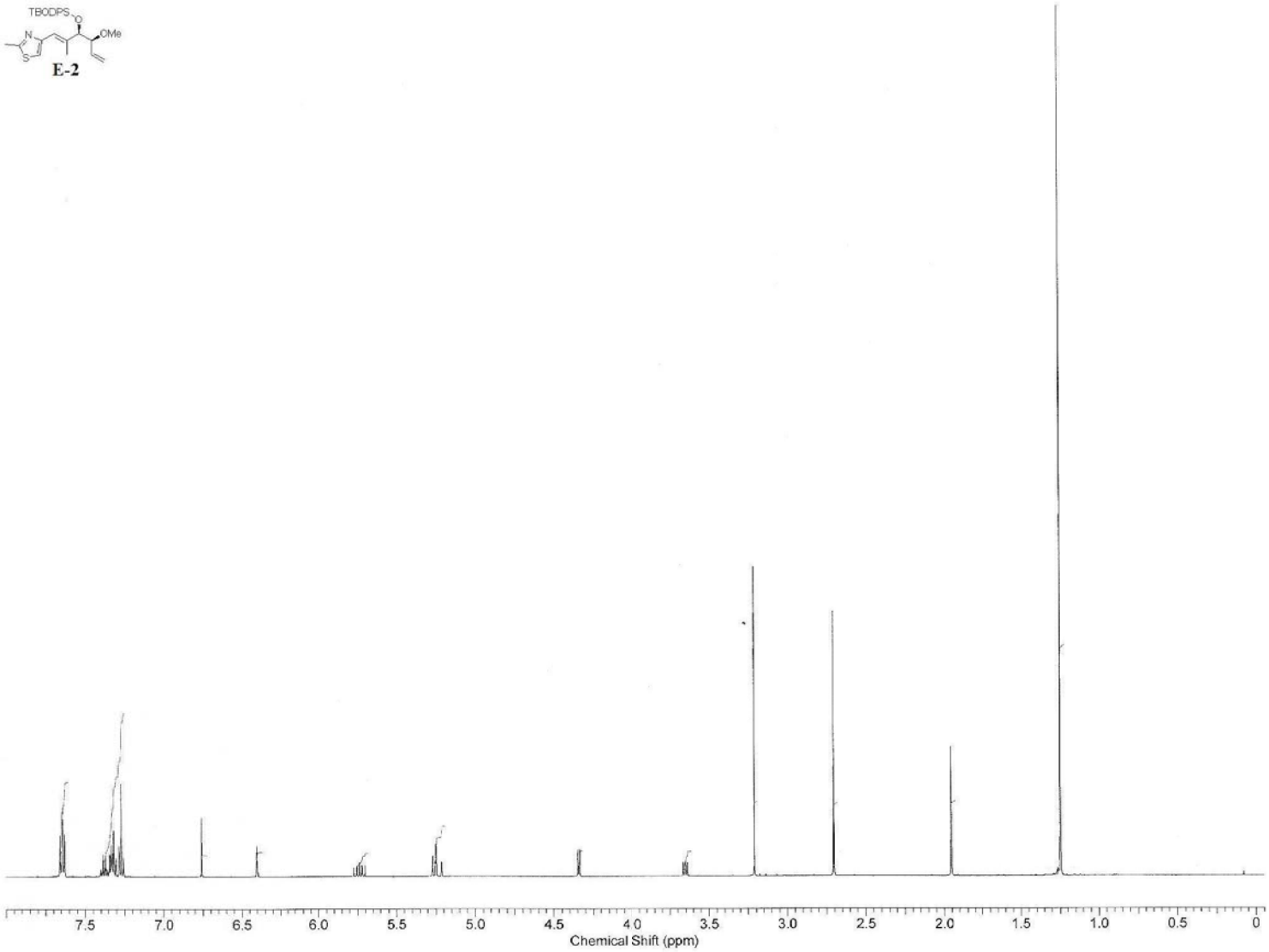
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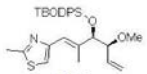
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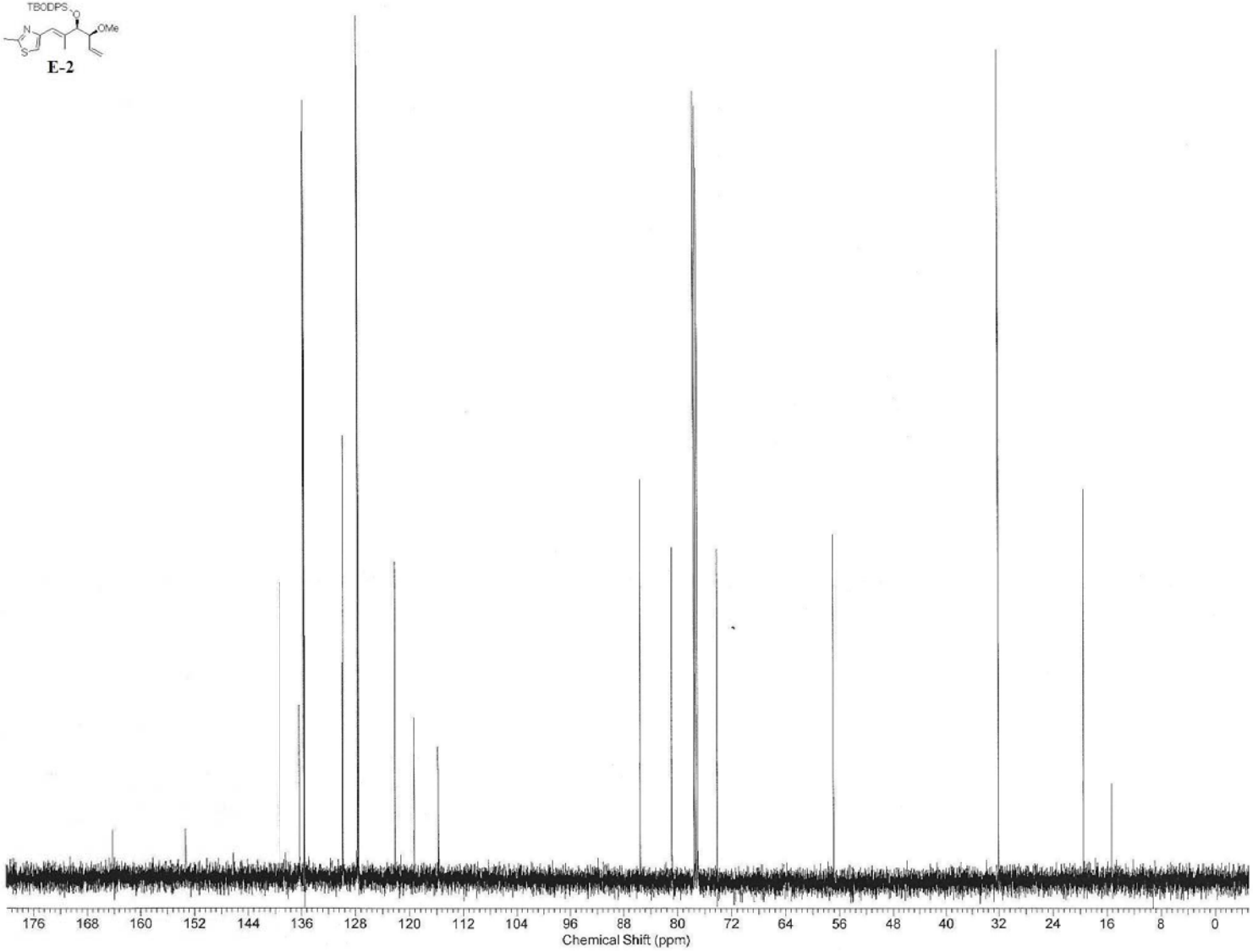
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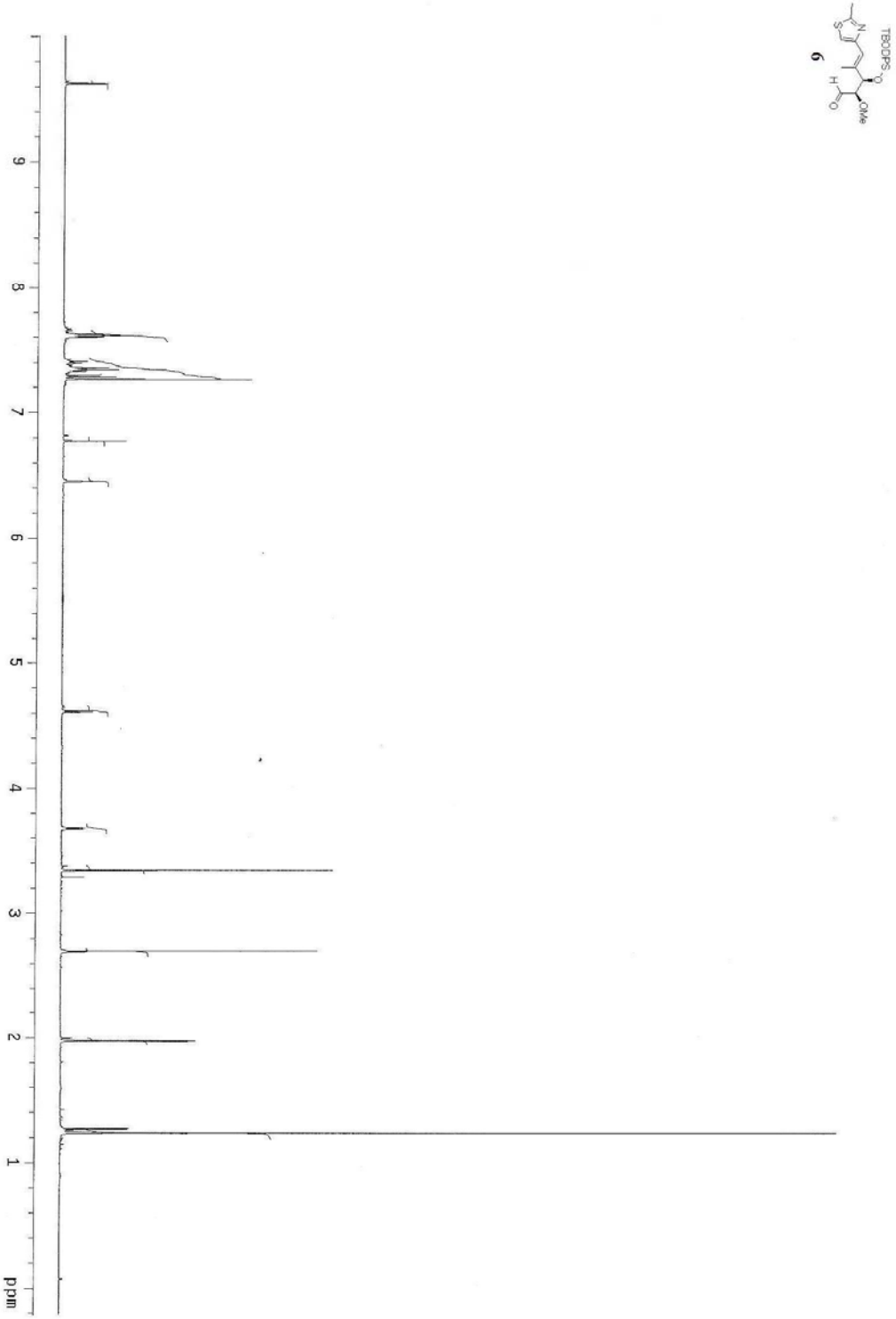
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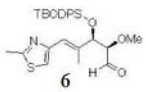

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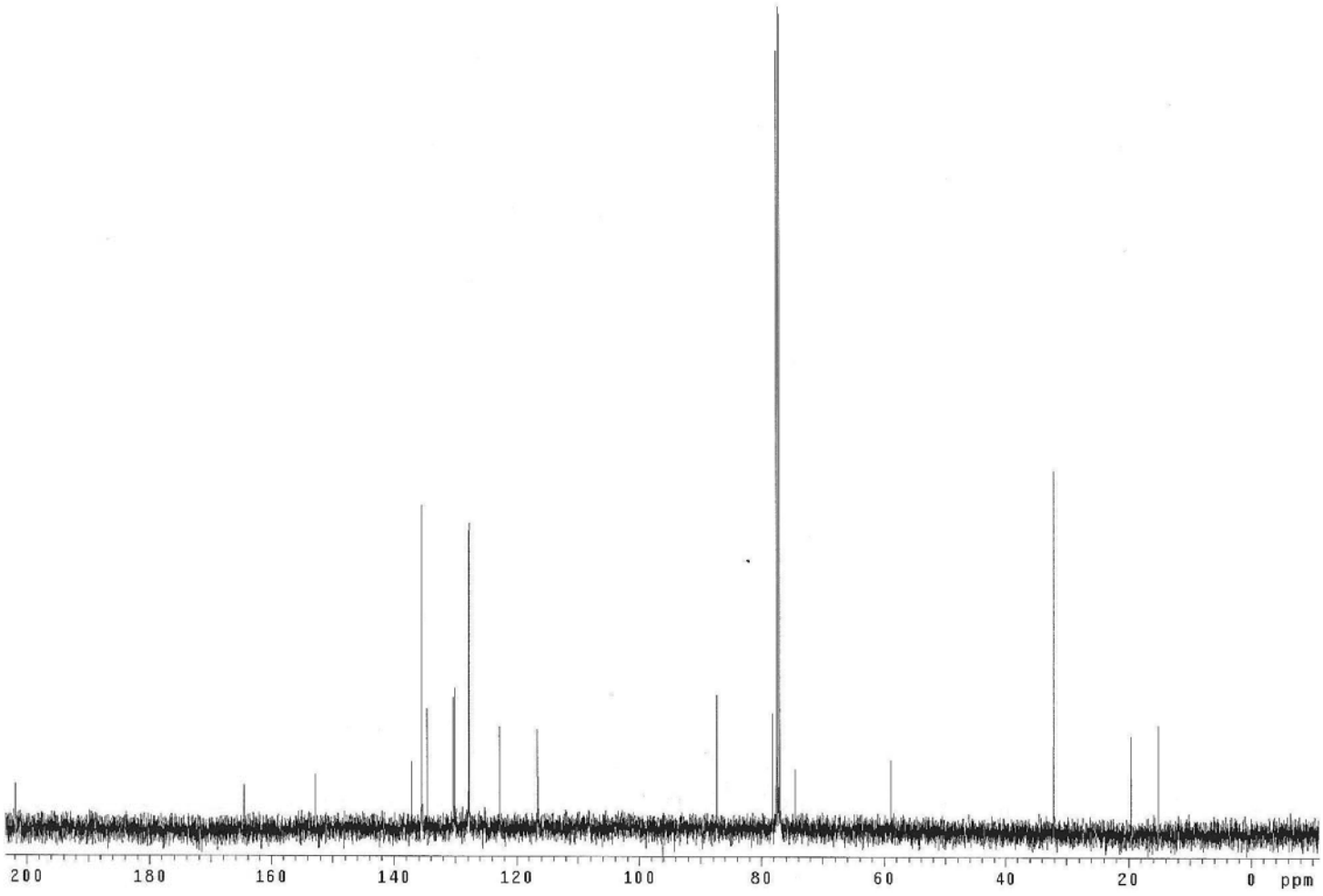
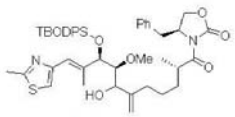
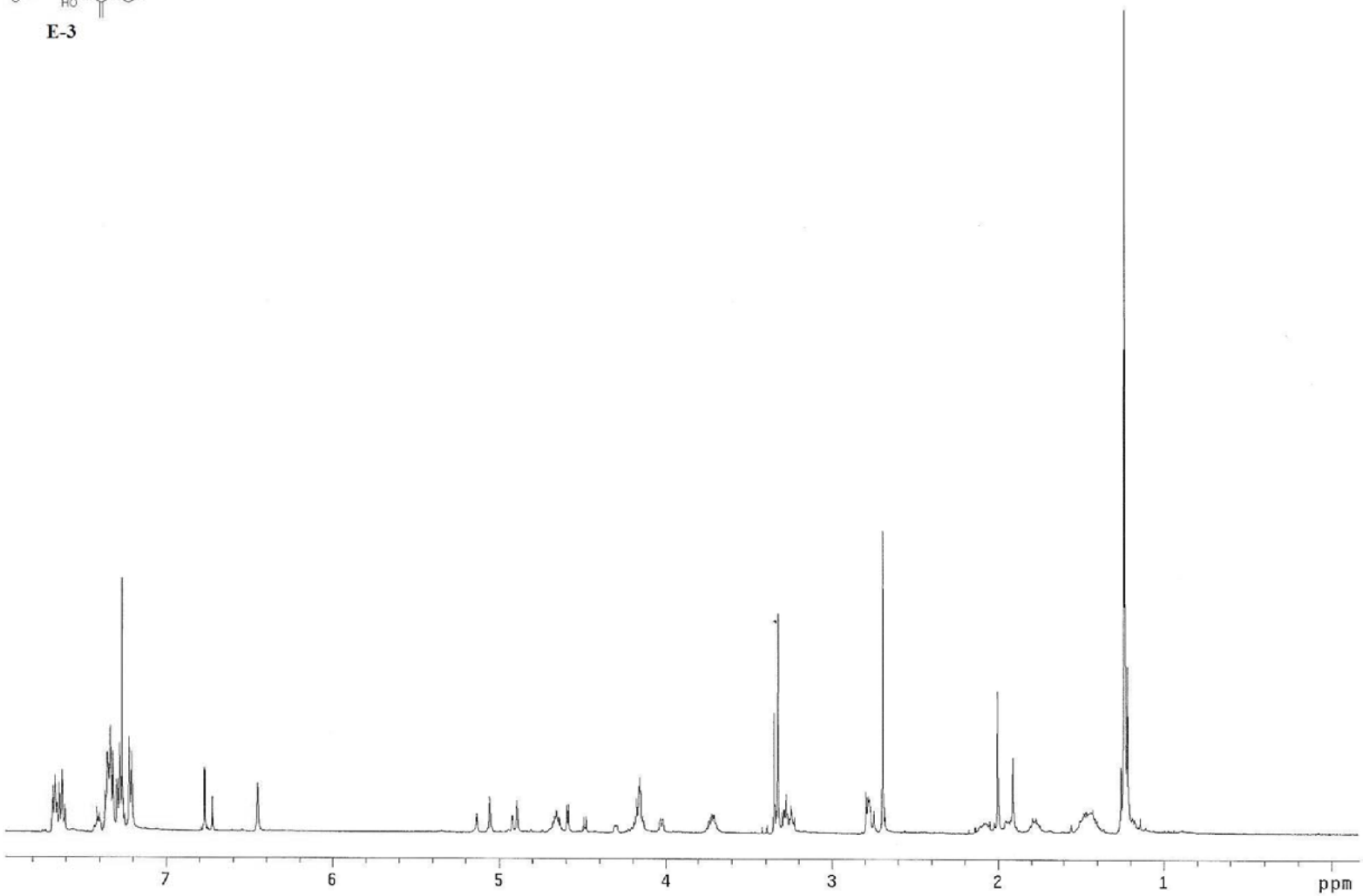
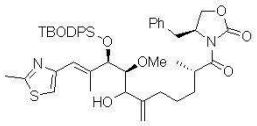


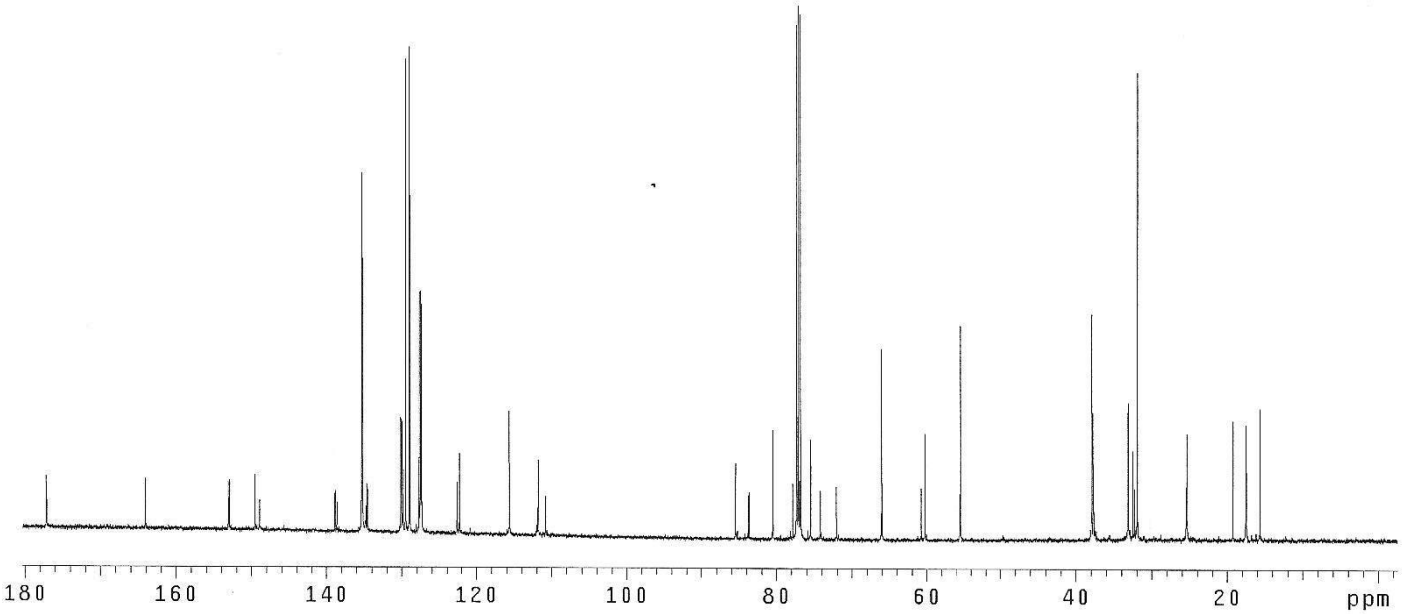


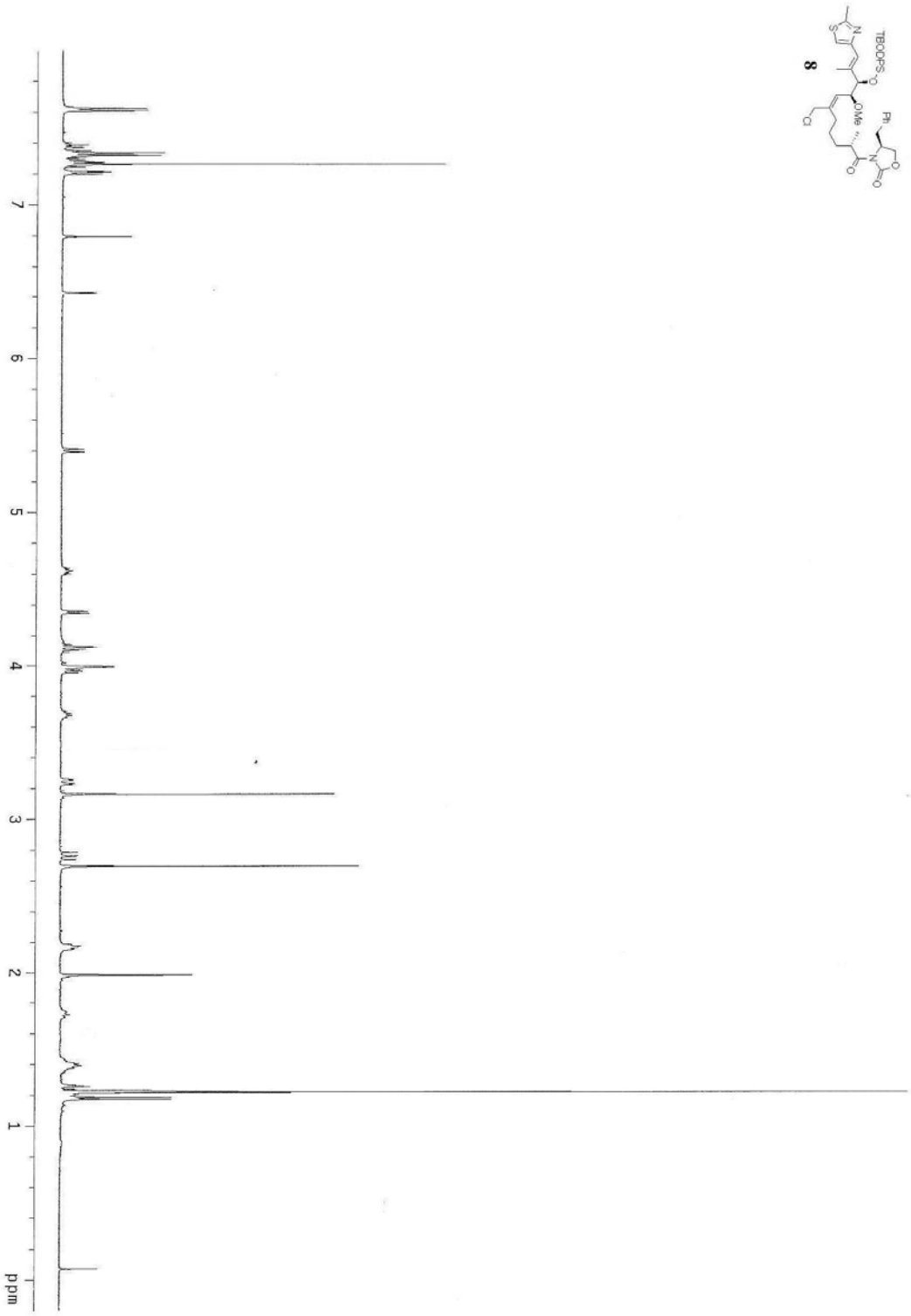
E-3

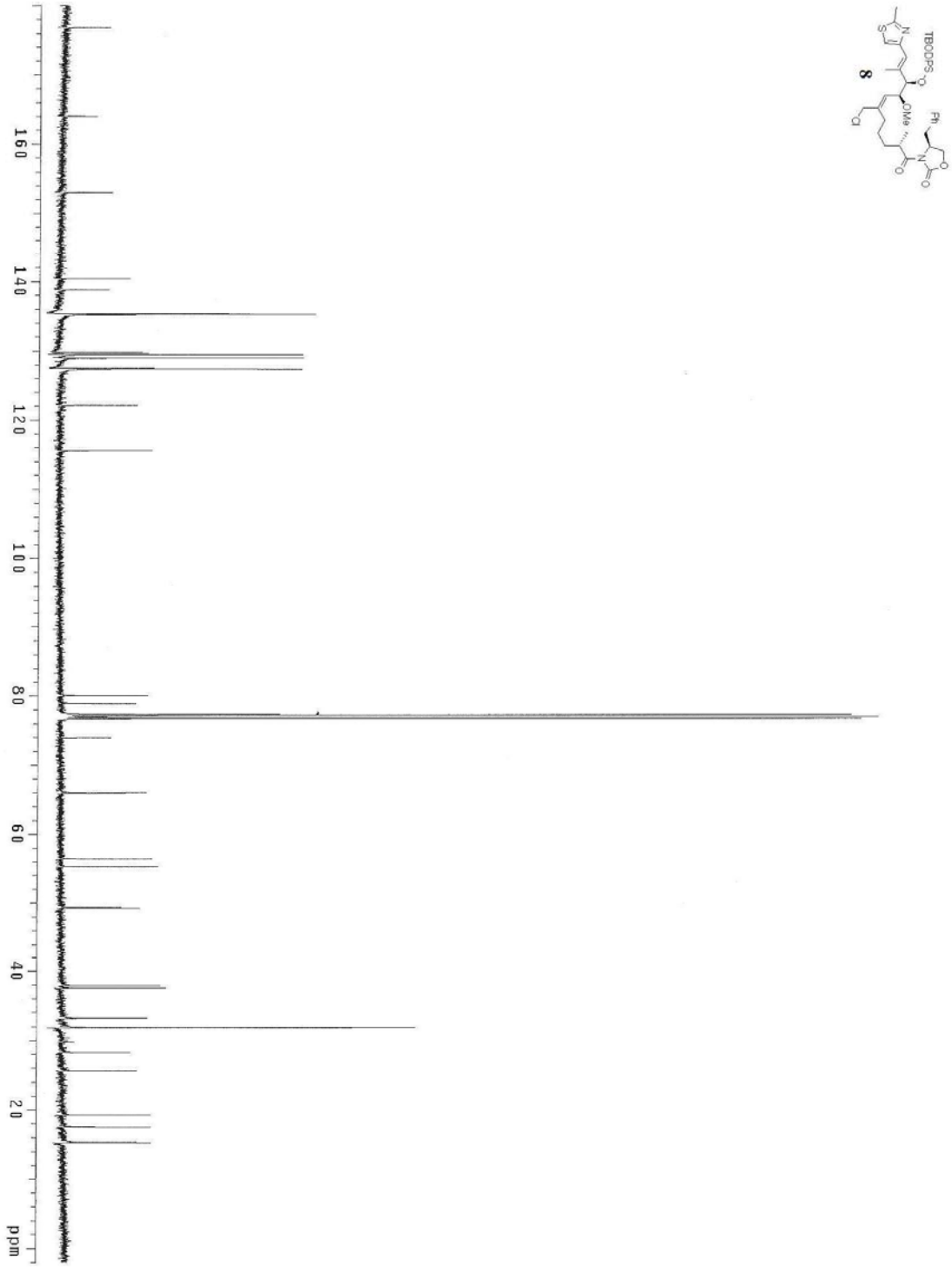


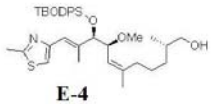


E-3

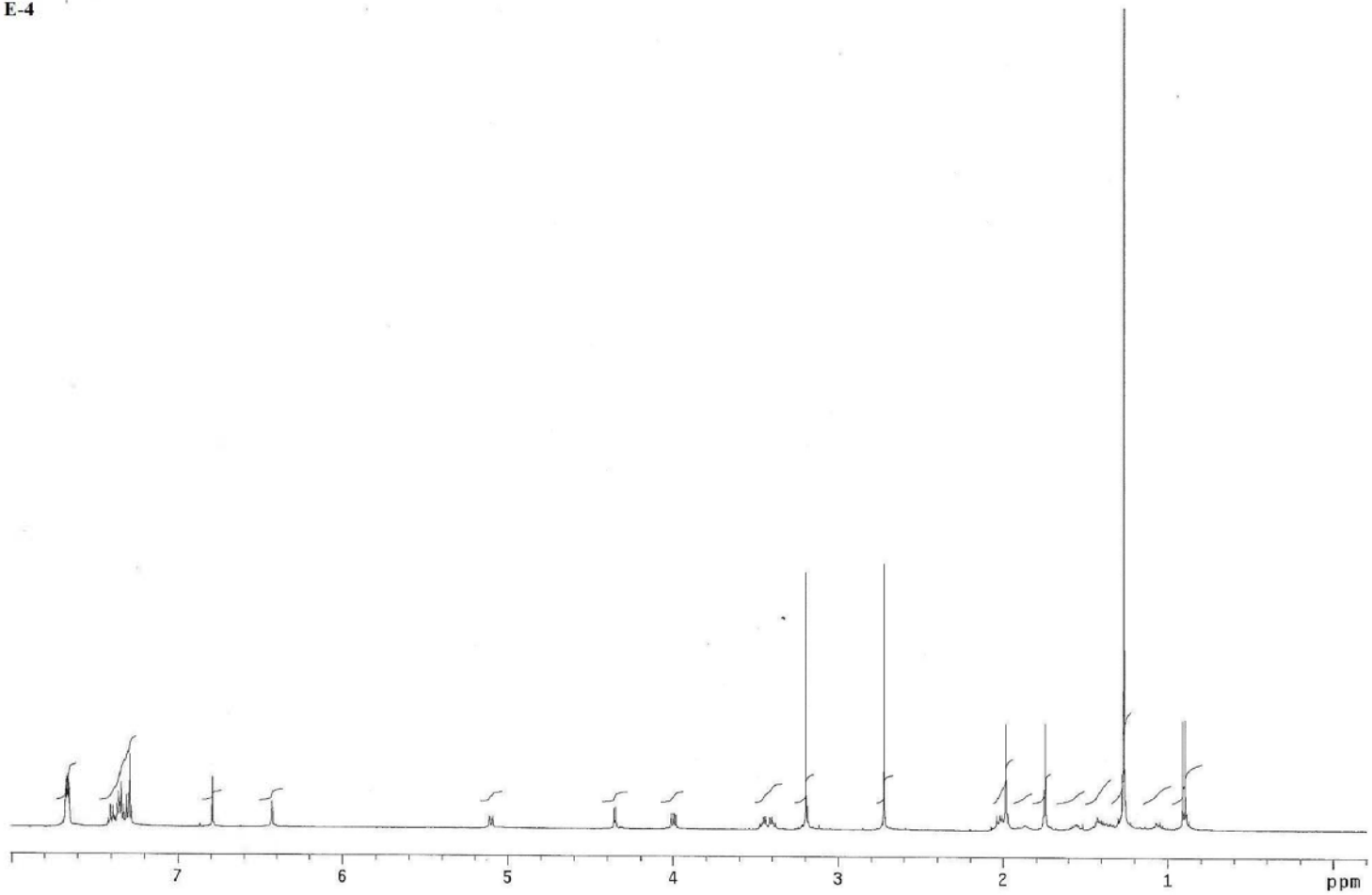


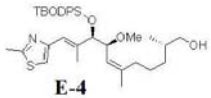

TBDPS
OMe
Pr
Cl
8
7
6
5
4
3
2
1
ppm


8
TBDPS
OMe
Ph
Cl
160
140
120
100
80
60
40
20
ppm

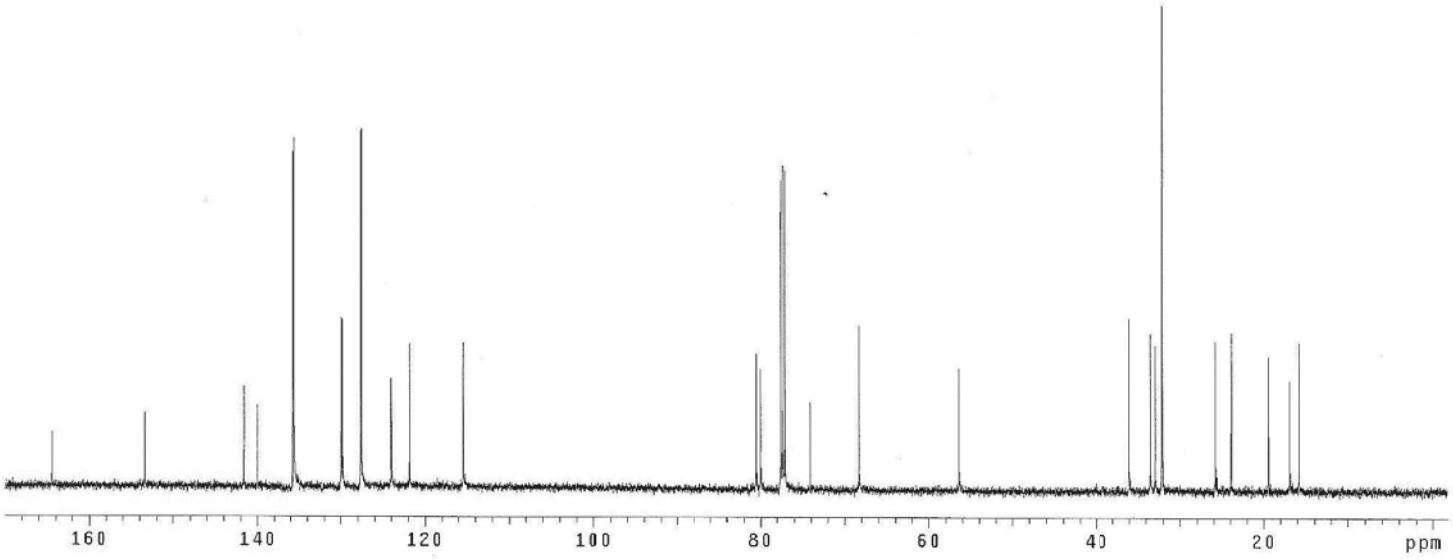


E-4





E-4



jf-3-98A-H-600MHz

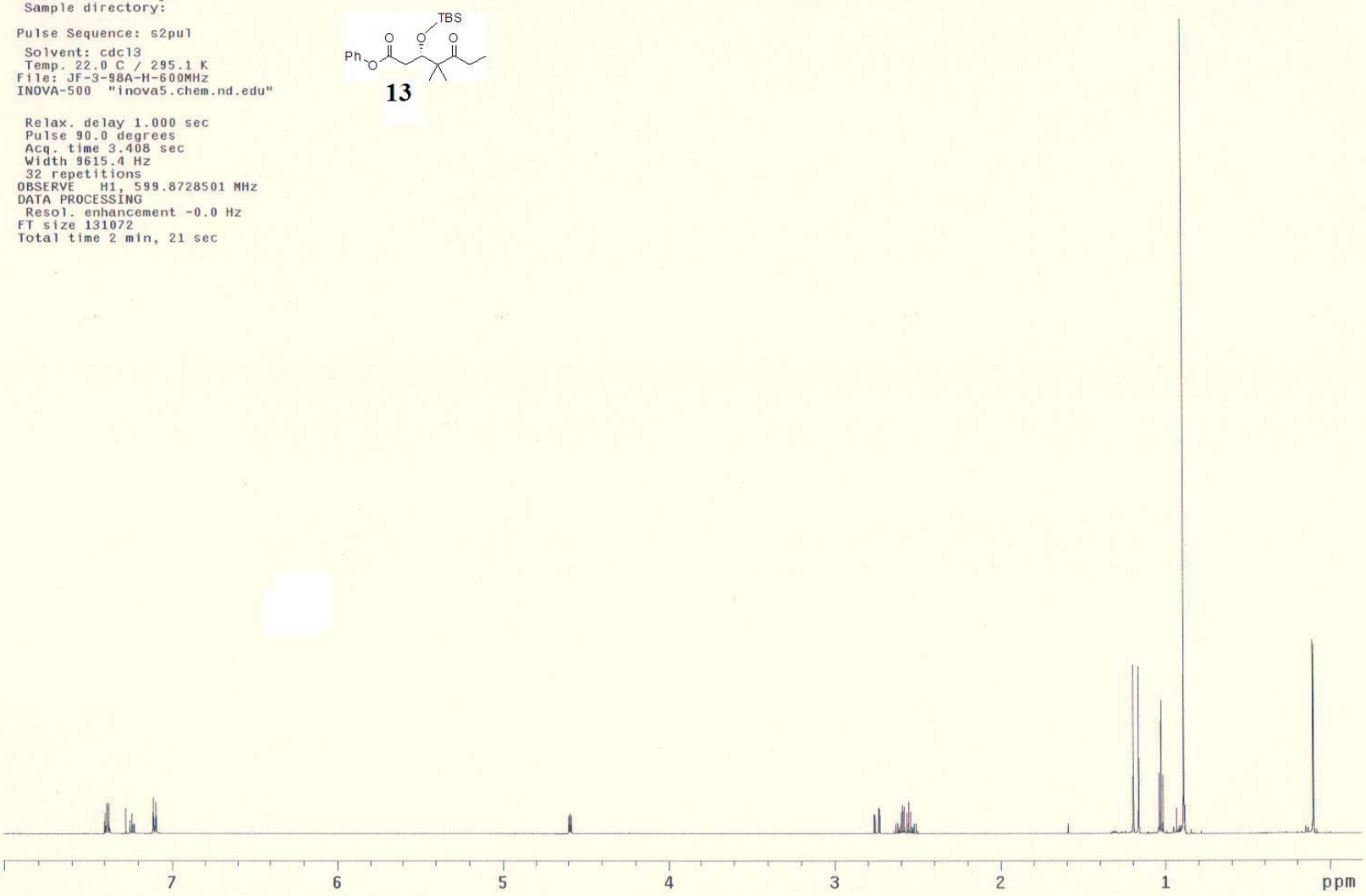
Archive directory:
Sample directory:

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 22.0 C / 295.1 K
File: JF-3-98A-H-600MHz
INOVA-500 "inova5.chem.nd.edu"

Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 3.408 sec
Width 9615.4 Hz
32 repetitions
OBSERVE H1, 599.8728501 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 131072
Total time 2 min, 21 sec

13



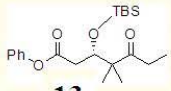
Std carbon

File: afs/nd.edu/user38

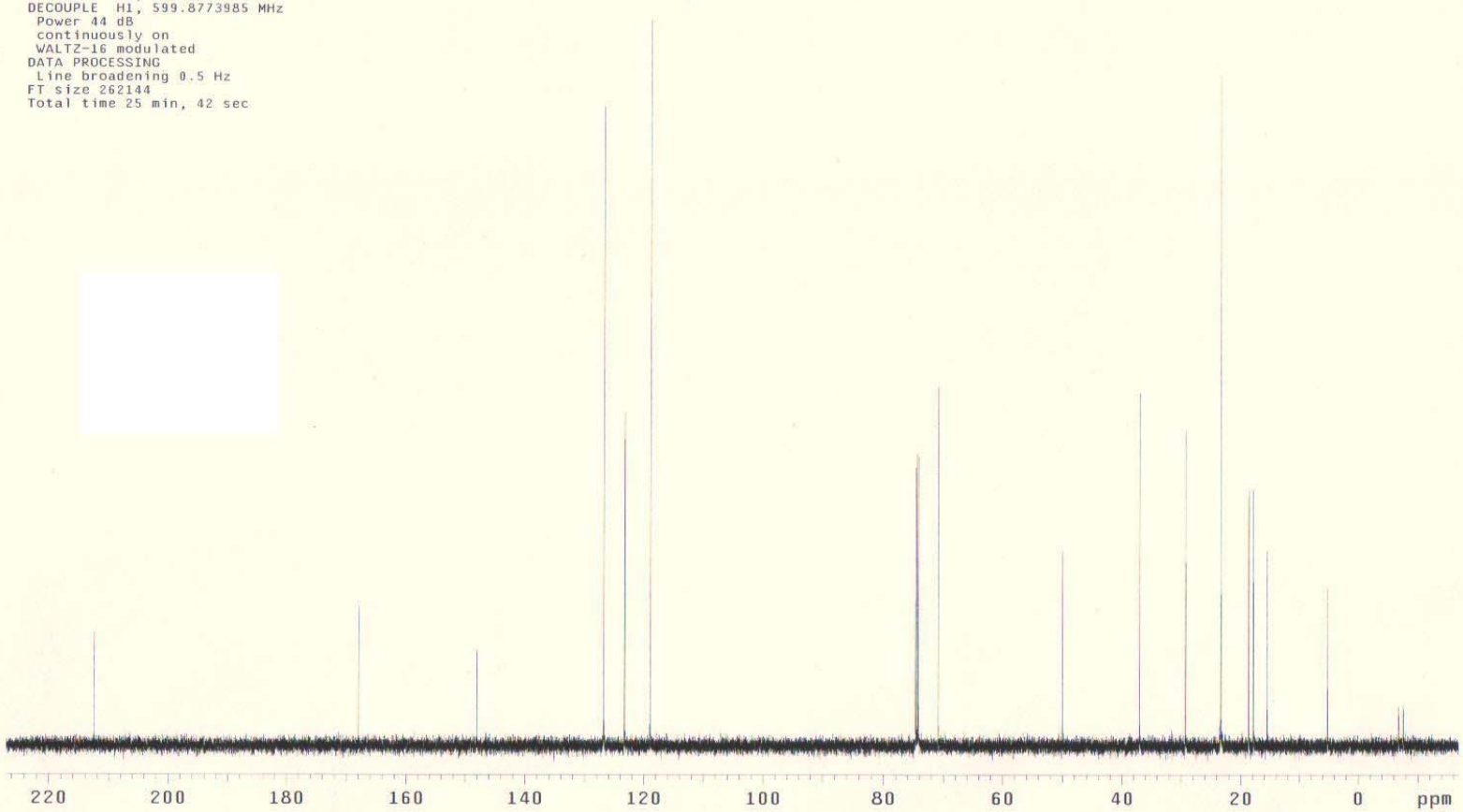
Pulse Sequence: s2pul

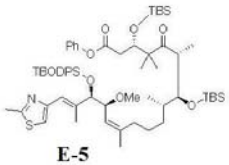
Solvent: D2O
Temp. 22.0 C / 295.1 K
Operator: vnmr1
File: JF-3-98A-C-600MHz
VNMRS-600 "nmr600"

Relax. delay 1.220 sec
Pulse 90.0 degrees
Acq. time 1.783 sec
Width 36764.7 Hz
68 repetitions
OBSERVE C13, 150.8385376 MHz
DECOUPLE H1, 599.8773985 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 262144
Total time 25 min, 42 sec

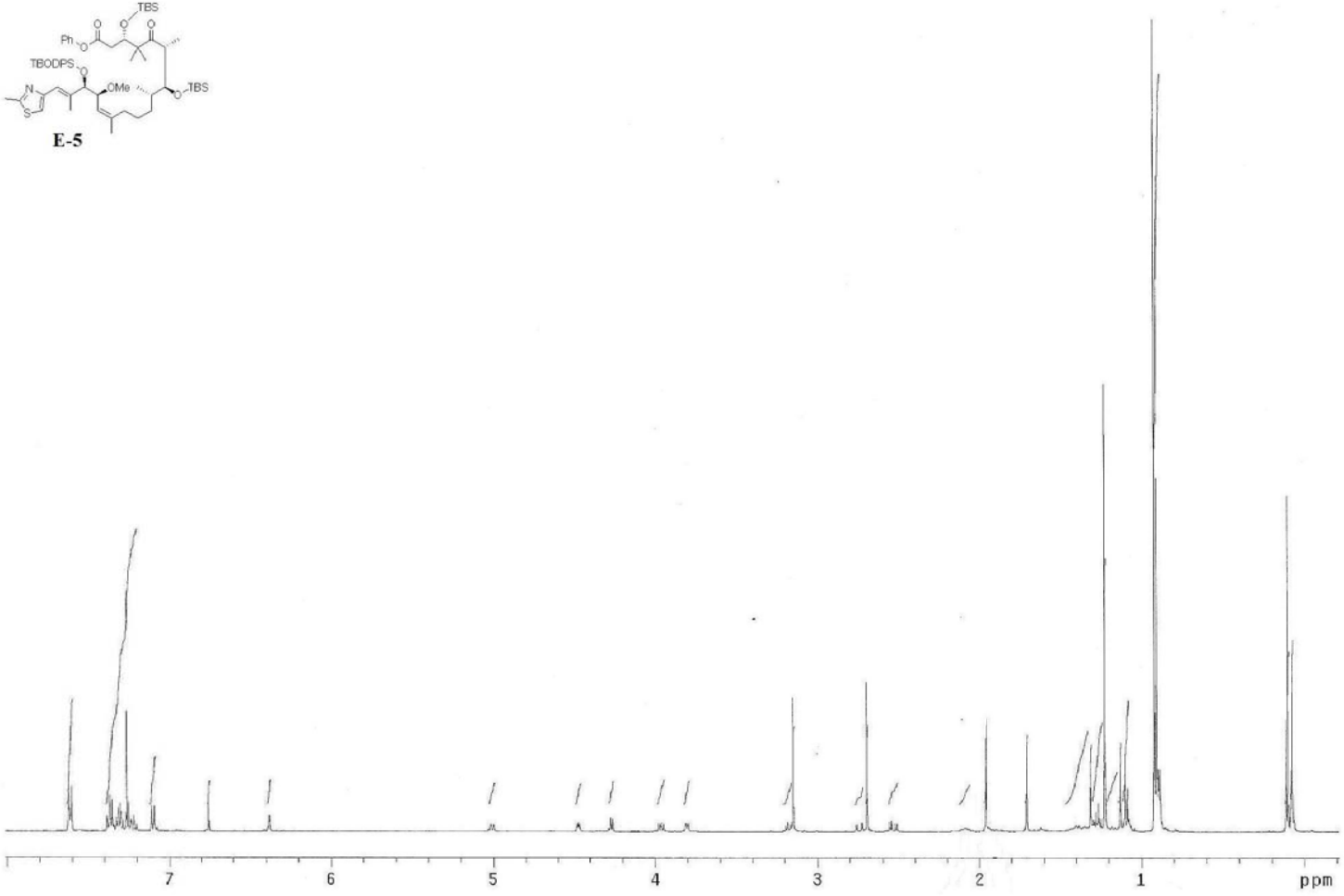


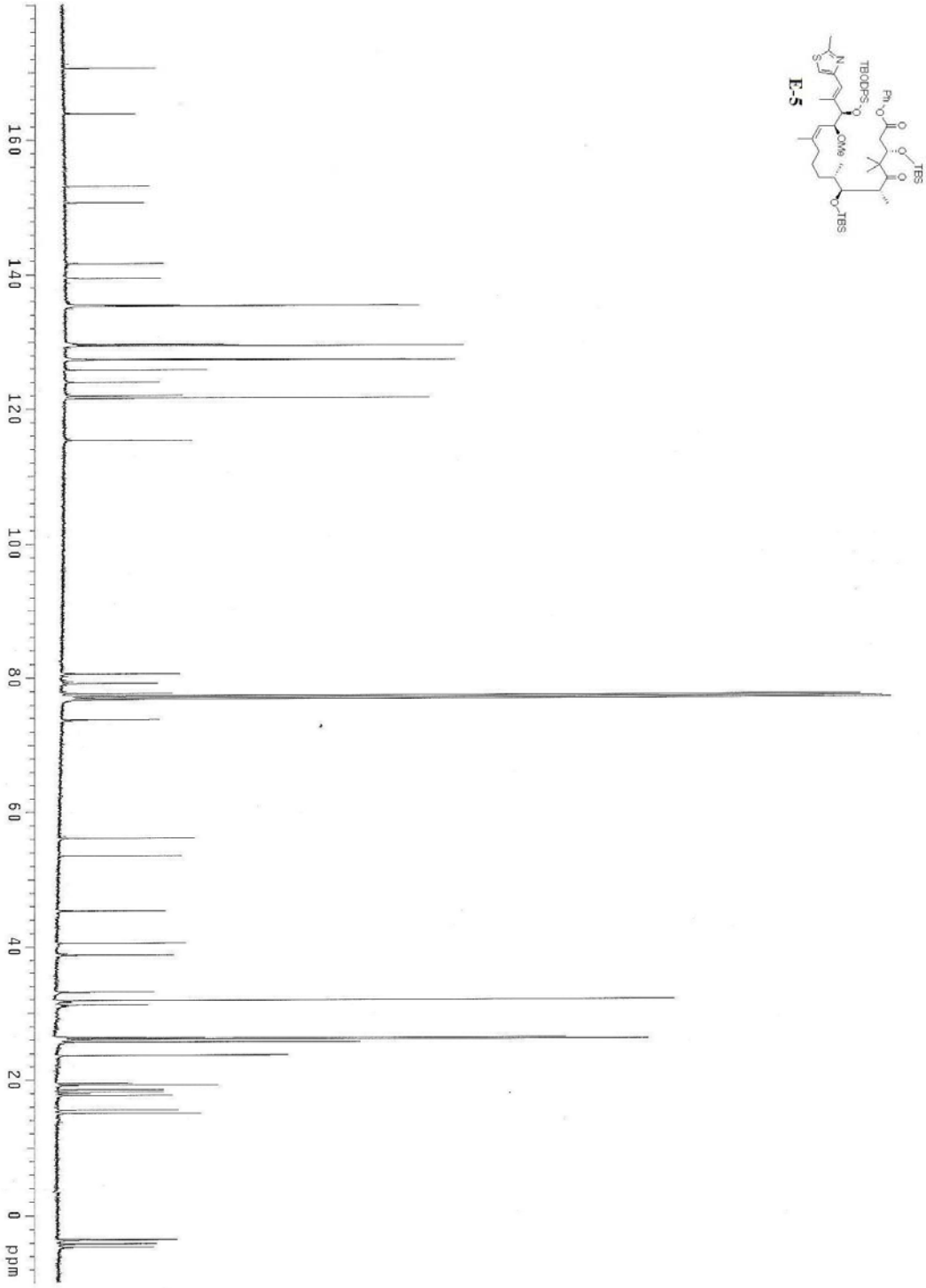
13





E-5




TBS
Ph
TBDPS
OMe
TBS
E-5
160
140
120
100
80
60
40
20
0
ppm

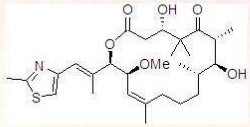
Std proton

Archive directory:
Sample directory:

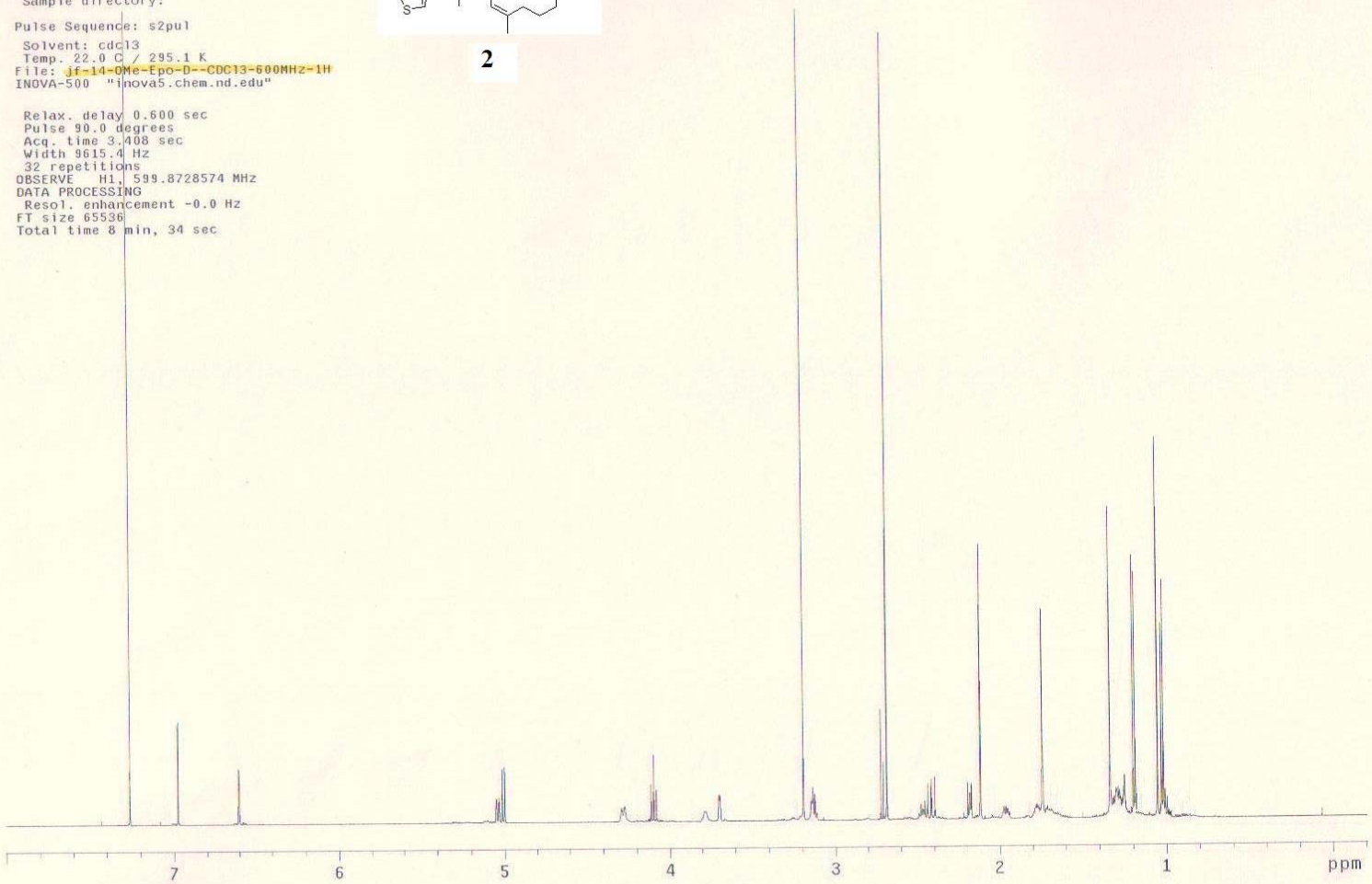
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 22.0 C / 295.1 K
File: jf-14-OMe-Epo-D--CDCl3-600MHz-1H
INOVA-500 "inova5.chem.nd.edu"

Relax. delay 0.600 sec
Pulse 90.0 degrees
Acq. time 3.408 sec
Width 9615.4 Hz
32 repetitions
OBSERVE H1, 599.8728574 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 8 min, 34 sec



2



Std carbon

Archive directory:
Sample directory:

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
User: 1-14-87
File: jf-14-OMe-Epo-D--CDCl3-600MHz-13C
INOVA-500 "inova5.chem.nd.edu"

Relax. delay 1.220 sec
Pulse 90.0 degrees
Acq. time 1.783 sec
Width 36764.7 Hz
24584 repetitions
OBSERVE C13, 150.8381500 MHz
DECOUPLE H1, 599.8758568 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 262144
Total time 83 hr, 39 min, 11 sec

2